To: Alison Andre[andre@ecohealthalliance.org]
Cc: Peter Daszak[daszak@ecohealthalliance.org]; Saif, Linda[saif.2@osu.edu]; tong.yigang |; fanhang majy2400@scau.edu.cn[majy2400@scau.edu.cn]; 博士石正丽[zlshi@wh.iov.cn]; peng.zhou@whiov.ac.cn[peng.zhou@whiov.ac.cn]; Baric, Ralph S[rbaric@email.unc.edu]; Wang, Qiuhong[wang.655@osu.edu]; 13520620736 Baric, Toni C[antoinette_baric@med.unc.edu]; Sims, Amy C[sims0018@email.unc.edu]; Kevin Olival[olival@ecohealthalliance.org]; Noam Ross[ross@ecohealthalliance.org]; Yasha Feferholtz[feferholtz@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Hongying Li[li@ecohealthalliance.org]
From: Wang Linfa[linfa.wang@duke-nus.edu.sg]
Sent: Wed 10/9/2019 8:55:40 AM (UTC-04:00)
Subject: Re: SADs-CoV Call - Wednesday Oct 9 at 8:00pm ET / Thursday Oct 10 at 8:00am China time

Singapore number?

Sent from my iPhone

On 9 Oct 2019, at 8:53 PM, Alison Andre <andre@ecohealthalliance.org> wrote:

Dear All,

We're confirmed for a call on Wednesday October 9th at 8:00pm Eastern time / Thursday October 10th at 8:00am China time. Please find the call in details below:

US:
China:

Passcode:

I will also send around a calendar invite.

Thank you,
Alison

Alison Andre
Executive Assistant to the President

EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(direct)
(fax)
www.ecohealthalliance.org

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Important: This email is confidential and may be privileged. If you are not the intended recipient, please delete it and notify us immediately; you should not copy or use it for any purpose, nor disclose its contents to any other person. Thank you.

To: Alison Andre[andre@ecohealthalliance.org]
Cc: Peter Daszak[daszak@ecohealthalliance.org]; Baric, Ralph S[rbaric@email.unc.edu]; Sims, Amy C[sims0018@email.unc.edu]; Wang Linfa[linfa.wang@duke-nus.edu.sg]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; ouihaagendazs ; gnyny0803]; Alice Latinne[latinne@ecohealthalliance.org]; Noam Ross[ross@ecohealthalliance.org]; Kevin Olival[olival@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Hongying Li[li@ecohealthalliance.org]; Baric, Toni C[antoinette_baric@med.unc.edu]; Luke Hamel[hamel@ecohealthalliance.org]; Lim Sandie[sandie.lim@duke-nus.edu.sg]
From: 任丽丽[renliliipb
Sent: Thur 10/17/2019 11:08:03 AM (UTC-04:00)
Subject: Re:NIAID SARs-CoV call - October 30/October 31

Dear Alison,
Thanks for the informatio. We will connect to the meeting center.
Best
Lili Ren

At 2019-10-17 21:36:38, "Alison Andre" <andre@ecohealthalliance.org> wrote:

Dear All,

Our NIAID SARs-Cov call has been scheduled for Wednesday October 30th at 8:00pm Eastern time (Thursday October 31st at 8:00am China/Singapore time).

Call in details:

US:
China:
Singapore:

Passcode:

Calendar invite to follow.

Thank you,
Alison

Alison Andre
Executive Assistant to the President

EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(direct)
(fax)
www.ecohealthalliance.org

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To: Baric, Ralph S[rbaric@email.unc.edu]
Cc: Hongying Li[li@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]
From: Peter Daszak[daszak@ecohealthalliance.org]
Sent: Tue 12/31/2019 9:02:59 AM (UTC-05:00)
Subject: RE: have you heard any news on this? maybe as many as 27 cases with 7 severe in wuhan--ards like pneumonia

Hongying's working on it right now to find out more information. She's just found a new report from a Wuhan Govt website that came out today and I'll forward that to you in a minute.

I've sent that on to ProMed also.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Baric, Ralph S [mailto:rbaric@email.unc.edu]
Sent: Tuesday, December 31, 2019 8:16 AM
To: Peter Daszak
Subject: RE: have you heard any news on this? maybe as many as 27 cases with 7 severe in wuhan--ards like pneumonia

Published Date: 2019-12-30 23:59:00
Subject: PRO/AH/EDR> Undiagnosed pneumonia - China (HU), RFI
Archive Number: 20191230.6864153
UNDIAGNOSED PNEUMONIA - CHINA (HUBEI), REQUEST FOR INFORMATION
****
A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

[1]
Date: 30 Dec 2019
Source: Finance Sina [machine translation]
https://finance.sina.cn/2019-12-31/detail-iihnzahk1074832.d.html?from=wap

Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

On the morning of [31 Dec 2019], China Business News reporter called the official hotline of Wuhan Municipal Health and Health Committee 12320 and learned that the content of the document is true.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

According to the above documents, according to the urgent notice from the superior, some medical institutions in Wuhan have successively appeared patients with pneumonia of unknown cause. All medical institutions should strengthen the management of outpatient and emergency departments, strictly implement the first-in-patient responsibility system, and find that patients with unknown cause of pneumonia actively adjust the power to treat them on the spot, and there should be no refusal to be pushed or pushed.

The document emphasizes that medical institutions need to strengthen multidisciplinary professional forces such as respiratory, infectious diseases, and intensive medicine in a targeted manner, open green channels, make effective connections between outpatient and emergency departments, and improve emergency plans for medical treatment.

Another piece of emergency notification, entitled "City Health and Health Commission's Report on Reporting the Treatment of Unknown Cause of Pneumonia" is also true. According to this document, according to the urgent notice from the superior, the South China Seafood Market in our city has seen patients with pneumonia of unknown cause one after another.

The so-called unexplained pneumonia cases refer to the following 4 cases of pneumonia that cannot be diagnosed at the same time: fever (greater than or equal to 38C); imaging characteristics of pneumonia or acute respiratory distress syndrome; reduced or normal white blood cells in the early stages of onset The number of lymphocytes was reduced. After treatment with antibiotics for 3 to 5 days, the condition did not improve significantly.

It is understood that the 1st patient with unexplained pneumonia that appeared in Wuhan this time came from Wuhan South China Seafood Market.

12320 hotline staff said that the Wuhan CDC went to the treatment hospital to collect patient samples as soon as possible, specifically what kind of virus is still waiting for the final test results. Patients with unexplained pneumonia have done a good job of isolation and treatment, which does not prevent other patients from going to the medical institution for medical treatment. Wuhan has the best virus research institution in the country, and the virus detection results will be released to the public as soon as they are found.

--
Communicated by:
ProMED-mail
<promed@promedmail.org>

To: Baric, Ralph S[rbaric@email.unc.edu]; Danielle Anderson (danielle.anderson@duke-nus.edu.sg)[danielle.anderson@duke-nus.edu.sg]; Wang Linfa[linfa.wang@duke-nus.edu.sg]
Cc: Hongying Li[li@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Kevin Olival[olival@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]
From: Peter Daszak[daszak@ecohealthalliance.org]
Sent: Tue 12/31/2019 9:10:06 AM (UTC-05:00)
Subject: FW: Wuhan Municipal Health Commission's briefing on the current pneumonia epidemic situation in the city

Hi All – Hongying translated the report from Mandarin – below…

We sent this on to ProMED just now, and I'm going to talk with Larry Madoff and others about it. Hongying is hearing from good sources that they have found a candidate virus in some samples and results will be sent out soon.

Cheers,

Peter

Peter Daszak
President

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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Hongying Li [mailto:li@ecohealthalliance.org]
Sent: Tuesday, December 31, 2019 8:32 AM
To: Peter Daszak
Cc: Aleksei Chmura; Alison Andre
Subject: Wuhan Municipal Health Commission's briefing on the current pneumonia epidemic situation in the city

Information from Wuhan Municipal Health Commission http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989

Wuhan Municipal Health Commission's briefing on the current pneumonia epidemic situation in the city, December 31, 2019

Recently, some of the pneumonia cases admitted in local medical institutions were found related to the South China Seafood Market. After receiving the report, the Municipal Health Commission immediately launched s and surveillance and retrospective investigation in the market and the city's medical and health institutions. Twenty-seven (27) cases have been identified, of which seven (7) are in serious condition, and the remaining cases are stable and controllable. Two (2) patients are expected to be discharged in the near future. The clinical symptoms were mainly fever, a few patients had difficulty breathing, and chest radiographs showed bilateral lung infiltrative lesions. At present, all cases have been quarantined for treatment, follow-up investigations and medical observations of people who have had close contacts with the patients are being conducted, and hygiene investigations and environmental sanitation disposals at South China Seafood Market are ongoing.

Wuhan city organized consultations with clinical medical, epidemiological, and virological experts from Tongji Hospital, Provincial CDC, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan Infectious Diseases Hospital, and Wuhan City CDC. According to the analysis of epidemiological investigations and preliminary laboratory tests, the above cases are considered to be viral pneumonia. Investigations so far have not revealed any apparent human-to-human transmission or infection by medical staff. Identification of the pathogen and investigation of the cause of the infection are ongoing.

Hongying Li, MPH 李泓萤
Research Scientist

EcoHealth Alliance
460 West 34th Street, Ste. 1701
New York, NY 10001

(U.S. mobile)
(Skype)
(WeChat)

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science, we develop solutions that promote conservation and prevent pandemics.

To: Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]
Cc: Kevin Olival[olival@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]; Baric, Ralph S[rbaric@email.unc.edu]
From: Peter Daszak[daszak@ecohealthalliance.org]
Sent: Sun 1/12/2020 12:34:54 PM (UTC-05:00)
Subject: RE: Wuhan Pneumonia

Thanks Erik – we've posted a phylogeny based on that and it's been circulating on the web now.

https://www.ecohealthalliance.org/2020/01/phylogenetic-analysis-shows-novel-wuhan-coronavirus-clusters-with-sars

Key points from our point of view:

- This novel virus falls within the SARS-CoV and SAR-related CoV clade, in contrast to statements put out by some of the Chinese groups that this is 'not related to SARS'
- It's close to SARr-CoV Rp3 that we published from our past NIAID work. This came from a Rhinolophus bat in S. China
- We have found antibodies to Rp3 in people in Yunnan Province previously, suggesting that these viruses are actively spilling over across a wider interface than currently known

You should also know that Ralph Baric (cc'd here) is already working to reconstruct and rescue the virus in the lab from the sequence, so he can do further work on it.

We'll keep you posted of course…

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Friday, January 10, 2020 10:30 PM
To: Peter Daszak
Subject: Re: Wuhan Pneumonia

Hi Peter,
We just received the fasta file with the sequence data, and I wanted to share it with you.

Erik

http://virological.org/t/initial-genome-release-of-novel-coronavirus/319

Sent from my iPhone
On Jan 8, 2020, at 11:08 PM, Peter Daszak <daszak@ecohealthalliance.org> wrote:

Erik – just to let you know that WSJ has now reported the novel CoV in 2 of the patients, citing “sources close to the investigation”. There are few details, and no more than I gave you today, so plenty of information still to wait for from our colleagues in China..

I’ve put out some tweets about it on @PeterDaszak if you want to take a look..

Cheers,

Peter

Peter Daszak
President

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New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Wednesday, January 8, 2020 3:22 PM
To: Alison Andre; Peter Daszak
Subject: RE: Wuhan Pneumonia

Great! I think the number I sent you should work. I’ll grab one of our conference rooms and sign in there. If not, the direct line to the conference room should be:

Thank you!
Erik

From: Alison Andre <andre@ecohealthalliance.org>
Sent: Wednesday, January 8, 2020 3:17 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Peter Daszak <daszak@ecohealthalliance.org>
Subject: Re: Wuhan Pneumonia

Hi Erik,

Just spoke to Peter and it would be great to have Dr. Embry join the call. Does the number still work for the both of you or would you like me to reserve a conference line?

Thanks,
Alison

From: "Stemmy, Erik (NIH/NIAID) [E]" <erik.stemmy@nih.gov>

Date: Wednesday, January 8, 2020 at 1:41 PM
To: Peter Daszak <daszak@ecohealthalliance.org>, Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Thanks Peter, me too. I'd mentioned our call to my branch chief, Dr Alan Embry. We'd been talking about your CoV work in Asia even before the news from Wuhan broke, and he's been interested in meeting you. Would you mind if he joined our call this afternoon as well? Seems like a good opportunity to make the introduction, but we can do it another time if you'd rather just speak with me.

Erik

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 4:24 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Look forward to talking with you tomorrow Erik…

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Tuesday, January 7, 2020 2:54 PM
To: Alison Andre; Peter Daszak
Subject: RE: Wuhan Pneumonia

Sure, that's perfect. He can reach me at .

Thanks!
Erik

From: Alison Andre <andre@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 2:52 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Peter Daszak <daszak@ecohealthalliance.org>
Subject: Re: Wuhan Pneumonia

Hi Erik,

Can Peter give you a call around 3:30 tomorrow? If that works for you, please let me know the best number to reach you on.

Thanks!
Alison

From: "Stemmy, Erik (NIH/NIAID) [E]" <erik.stemmy@nih.gov>
Date: Tuesday, January 7, 2020 at 2:49 PM
To: Peter Daszak <daszak@ecohealthalliance.org>
Cc: Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

That would be great! Thank you for getting back to me. I wasn't sure if you were traveling or not, so I'd also reached out to Aleksei. I can be pretty flexible tomorrow, so just let me know what time works for you.

Very much appreciate your time!
Erik

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 2:48 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>
Cc: Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Definitely focusing attention on this Erik – I spent New Year's Eve talking with our China contacts, and with ProMED staff between glasses!

I've got more information, but it's all off the record. Could I give you a call tomorrow to fill you in? I've cc'd Alison Andre who can arrange a time that works for a quick call….

Cheers,

Peter

Peter Daszak
President

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New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Monday, January 6, 2020 7:28 AM
To: Peter Daszak

Subject: Wuhan Pneumonia

Hi Peter,
Happy New Year! I'm sure you've been following along with the Wuhan pneumonia cases, and I wanted to see if you had any information from your contacts over there. I saw SARS and MERS had been ruled out, but curious to know if there's any indication you've seen that another bat CoV might be involved.

Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone:
Email: erik.stemmy@nih.gov

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To: Degrace, Marciela (NIH/NIAID) [E][marciela.degrace@nih.gov]; Webby, Richard[Richard.Webby@STJUDE.ORG]; malik[malik@hku.hk]; Ghazi Kayali[ghazi@human-link.org]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; 'adolfo.garcia-sastre@mssm.edu'[adolfo.garcia-sastre@mssm.edu]; Richard Rothman[rrothma1@jhmi.edu]; Pekosz, Andrew S. (apekosz@jhsph.edu)[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@STJUDE.ORG]; 'david_topham@urmc.rochester.edu'[david_topham@urmc.rochester.edu]; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'Perlman, Stanley'[stanley-perlman@uiowa.edu]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; Post, Diane (NIH/NIAID) [E][postd@niaid.nih.gov]; lsauer2@jhmi.edu[lsauer2@jhmi.edu]
Cc: Ryan Camping[ryan.camping@mssm.edu]; Melissa Uccellini[melissa.uccellini@mssm.edu]; McKenzie, Pamela[Pamela.McKenzie@STJUDE.ORG]; Neu, Donna[Donna_Neu@URMC.Rochester.edu]; Kathryn Shaw-Saliba[kshaw15@jhu.edu]; Collins, Erin-Joi[emcneal@emory.edu]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]; Andy Pekosz[apekosz1@jhu.edu]
From: Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]
Sent: Mon 1/13/2020 1:52:50 PM (UTC-05:00)
Subject: RE: Wuhan Pneumonia response

Wuhan Pneumonia response

Tue, Jan 14, 2020 10:00 AM - 11:00 AM (EST)

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Costa Rica (Toll Free): 0800 542 5405
Czech Republic (Toll Free): 800 500448
Denmark (Toll Free): 8025 2661
Denmark: +45 32 72 03 82
Finland (Toll Free): 0 800 917656
Finland: +358 923 17 0568
France (Toll Free): 0 805 541 047
France: +33 170 950 594
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Germany: +49 692 5736 7317
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Hong Kong (Toll Free): 30713169
Hungary (Toll Free): (06) 80 986 255
Iceland (Toll Free): 800 7204
India (Toll Free): 18002669254
Indonesia (Toll Free): 007 803 020 5375
Ireland (Toll Free): 1 800 901 610
Ireland: +353 15 360 728
Israel (Toll Free): 1 809 454 830

Italy (Toll Free): 800 793887
Italy: +39 0 230 57 81 42
Japan (Toll Free): 0 120 663 800
Korea, Republic of (Toll Free): 00798 14 207 4914
Luxembourg (Toll Free): 800 85158
Malaysia (Toll Free): 1 800 81 6854
Mexico (Toll Free): 01 800 522 1133
Mexico: +52 55 3687 7278
Netherlands (Toll Free): 0 800 020 0182
Netherlands: +31 207 941 377
New Zealand (Toll Free): 0 800 44 5550
New Zealand: +64 9 280 6302
Norway (Toll Free): 800 69 046
Norway: +47 21 93 37 51
Panama (Toll Free): 00 800 226 7928
Peru (Toll Free): 0 800 77023
Philippines (Toll Free): 1 800 1110 1661
Poland (Toll Free): 00 800 1124759
Portugal (Toll Free): 800 819 575
Romania (Toll Free): 0 800 400 819
Russian Federation (Toll Free): 8 800 100 6203
Saudi Arabia (Toll Free): 800 844 3633
Singapore (Toll Free): 18007231323
Slovakia (Toll Free): 0 800 105 748
South Africa (Toll Free): 0 800 555 447
Spain (Toll Free): 800 900 582
Spain: +34 932 75 2004
Sweden (Toll Free): 0 200 330 905
Sweden: +46 853 527 836
Switzerland (Toll Free): 0 800 002 348
Switzerland: +41 225 4599 78
Taiwan (Toll Free): 0 800 666 854
Thailand (Toll Free): 001 800 658 131
Turkey (Toll Free): 00 800 4488 23683
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https://global.gotomeeting.com/install/520152733

From: Degrace, Marciela (NIH/NIAID) [E]
Sent: Saturday, January 11, 2020 7:24 AM
To: 'Webby, Richard' <Richard.Webby@STJUDE.ORG>; 'malik' <malik@hku.hk>; 'Ghazi Kayali' <ghazi@human-link.org>; 'Yoshi Kawaoka' <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; 'adolfo.garcia-sastre@mssm.edu' <adolfo.garcia-sastre@mssm.edu>; 'Richard Rothman' <rrothma1@jhmi.edu>; 'Pekosz, Andrew S. (apekosz@jhsph.edu)' <apekosz@jhsph.edu>; 'Schultz-Cherry, Stacey' <Stacey.Schultz-Cherry@STJUDE.ORG>; 'david_topham@urmc.rochester.edu' <david_topham@urmc.rochester.edu>; 'Orenstein, Walter' <worenst@emory.edu>; 'Lowen, Anice' <anice.lowen@emory.edu>
Cc: 'ryan.camping@mssm.edu' <ryan.camping@mssm.edu>; 'Melissa Uccellini' <melissa.uccellini@mssm.edu>; 'McKenzie, Pamela' <Pamela.McKenzie@STJUDE.ORG>; 'Neu, Donna' <Donna_Neu@URMC.Rochester.edu>; 'Kathryn Shaw-Saliba' <kshaw15@jhu.edu>; 'Collins, Erin-Joi' <emcneal@emory.edu>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>
Subject: RE: Wuhan Pneumonia response - setting up a call
Importance: High

Hi everyone,

Thanks for your responses to the poll. It looks like **Tuesday January 14th at 10am ET** will be the best time to meet. I'll send a

placeholder invitation shortly with call-in information to follow.

Also, please see below:
http://virological.org/t/initial-genome-release-of-novel-coronavirus/319

Marciela

From: Degrace, Marciela (NIH/NIAID) [E]
Sent: Thursday, January 9, 2020 2:11 PM
To: Webby, Richard <Richard.Webby@STJUDE.ORG>; malik <malik@hku.hk>; Ghazi Kayali <ghazi@human-link.org>; Yoshi Kawaoka <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; adolfo.garcia-sastre@mssm.edu; Richard Rothman <rrothma1@jhmi.edu>; Pekosz, Andrew S. (apekosz@jhsph.edu) <apekosz@jhsph.edu>; Schultz-Cherry, Stacey <Stacey.Schultz-Cherry@STJUDE.ORG>; david_topham@urmc.rochester.edu; Orenstein, Walter <worenst@emory.edu>; Lowen, Anice <anice.lowen@emory.edu>
Cc: ryan.camping@mssm.edu; Melissa Uccellini <melissa.uccellini@mssm.edu>; McKenzie, Pamela <Pamela.McKenzie@STJUDE.ORG>; Neu, Donna <Donna_Neu@URMC.Rochester.edu>; Kathryn Shaw-Saliba <kshaw15@jhu.edu>; Collins, Erin-Joi <emcneal@emory.edu>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>
Subject: Wuhan Pneumonia response - setting up a call
Importance: High

Hi all,

As you all have heard, China is reporting a novel coronavirus is causing viral pneumonia in Wuhan. While we have very little information at this point, NIAID leadership would like to begin thinking about how we would perform a research response should the outbreak continue and we get access to samples. We would like to hear what you think would be important research directions to pursue to start as well as the capabilities your groups may have given what is known at the moment. We can also discuss potential resources needed from NIAID by your groups so that we can prepare on this end to help you all if needed.

We will look to add some additional coronavirus experts to the call, and if there's anyone I haven't copied here from CEIRS that you think should be involved, please let me know. We need to move quickly, so the goal is to have a call next week at the time when most people are available.

Below is a doodle poll to find a time. Please fill out by the **end of the day tomorrow** so we can schedule a time accordingly.

I know it is already such a busy time – but I'm hopeful since we know the drill for these sorts of things that preparing now will help us.

Thank you all, and looking forward to getting your feedback and input.

Marciela

(Coordinators – this is FYI only and for scheduling, you don't have to be on the call)

To: Baric, Ralph S[rbaric@email.unc.edu]
Cc: Alison Andre[andre@ecohealthalliance.org]
From: Peter Daszak[daszak@ecohealthalliance.org]
Sent: Mon 1/13/2020 7:55:43 PM (UTC-05:00)
Subject: RE: Call with NIH tomorrow

OK - great. It sounds like we're on the same call!

And my thoughts exactly re. the highly variable SARS-like CoV. I've told journalists about it, but it's a complicated story for them to get across..

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

-----Original Message-----
From: Baric, Ralph S [mailto:rbaric@email.unc.edu]
Sent: Monday, January 13, 2020 6:50 PM
To: Peter Daszak
Subject: RE: Call with NIH tomorrow

Hi Peter, I have to participate on an NIH call tomorrow at 10. I believe it's a strategic meeting designed to help craft a NIH response plan to the WU-CoV. Hope things are going well. Looks like we found our highly variable SARS-like CoV! Ralph

-----Original Message-----
From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Monday, January 13, 2020 6:43 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Sims, Amy C <sims0018@email.unc.edu>
Cc: Alison Andre <andre@ecohealthalliance.org>
Subject: Call with NIH tomorrow

Ralph - I'm having an informational call with our program officer re the Wuhan outbreak tomorrow at 10am - do you want to join and are you available?

No prob if you can’t - I did one last week just to let them know what we think is going on behind the scenes in China.

Cheers,

Peter

Peter Daszak
(Sent from my iPhone)

President
EcoHealth Alliance

460 West 34th Street, New York, NY10001, USA

www.EcoHealthAlliance.org

To: Peter Daszak[daszak@ecohealthalliance.org]
Cc: Kevin Olival[olival@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]; Baric, Ralph S[rbaric@email.unc.edu]
From: Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]
Sent: Tue 1/14/2020 8:16:50 AM (UTC-05:00)
Subject: RE: Wuhan Pneumonia

Thanks! Yes, I'll be on the 10am call as well.

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, January 14, 2020 8:15 AM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>
Cc: Kevin Olival <olival@ecohealthalliance.org>; Robert Kessler <kessler@ecohealthalliance.org>; Baric, Ralph <rbaric@email.unc.edu>
Subject: RE: Wuhan Pneumonia

Not yet re. samples closer to Wuhan for Rp3-like CoVs.

I think the concern is that there is probably a low level exposure to these bat-origin viruses across southern and central China.

I'll be on the call at 10 am today – will you be?

Cheers,

Peter

Peter Daszak
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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Monday, January 13, 2020 7:46 AM
To: Peter Daszak
Cc: Kevin Olival; Robert Kessler; Baric, Ralph
Subject: Re: Wuhan Pneumonia

Thanks Peter. That's good to know. Have you also checked for Rp3 in samples from places closer to Wuhan?

Sent from my iPhone
On Jan 12, 2020, at 12:35 PM, Peter Daszak <daszak@ecohealthalliance.org> wrote:

> Thanks Erik – we've posted a phylogeny based on that and it's been circulating on the web now.

https://www.ecohealthalliance.org/2020/01/phylogenetic-analysis-shows-novel-wuhan-coronavirus-clusters-with-sars

Key points from our point of view:

- This novel virus falls within the SARS-CoV and SAR-related CoV clade, in contrast to statements put out by some of the Chinese groups that this is 'not related to SARS'
- It's close to SARr-CoV Rp3 that we published from our past NIAID work. This came from a Rhinolophus bat in S. China
- We have found antibodies to Rp3 in people in Yunnan Province previously, suggesting that these viruses are actively spilling over across a wider interface than currently known

We'll keep you posted of course…

Cheers,

Peter

Peter Daszak
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Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Friday, January 10, 2020 10:30 PM
To: Peter Daszak
Subject: Re: Wuhan Pneumonia

Hi Peter,
We just received the fasta file with the sequence data, and I wanted to share it with you.

Erik

http://virological.org/t/initial-genome-release-of-novel-coronavirus/319

Sent from my iPhone
On Jan 8, 2020, at 11:08 PM, Peter Daszak <daszak@ecohealthalliance.org> wrote:

Erik – just to let you know that WSJ has now reported the novel CoV in 2 of the patients, citing "sources

close to the investigation". There are few details, and no more than I gave you today, so plenty of information still to wait for from our colleagues in China..

I've put out some tweets about it on @PeterDaszak if you want to take a look..

Cheers,

Peter

Peter Daszak
President

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New York, NY 10001

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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Wednesday, January 8, 2020 3:22 PM
To: Alison Andre; Peter Daszak
Subject: RE: Wuhan Pneumonia

Great! I think the number I sent you should work. I'll grab one of our conference rooms and sign in there. If not, the direct line to the conference room should be:

Thank you!
Erik

From: Alison Andre <andre@ecohealthalliance.org>
Sent: Wednesday, January 8, 2020 3:17 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Peter Daszak <daszak@ecohealthalliance.org>
Subject: Re: Wuhan Pneumonia

Hi Erik,

Just spoke to Peter and it would be great to have Dr. Embry join the call. Does the number still work for the both of you or would you like me to reserve a conference line?

Thanks,
Alison

From: "Stemmy, Erik (NIH/NIAID) [E]" <erik.stemmy@nih.gov>
Date: Wednesday, January 8, 2020 at 1:41 PM
To: Peter Daszak <daszak@ecohealthalliance.org>, Alison Andre

<andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Thanks Peter, me too. I'd mentioned our call to my branch chief, Dr Alan Embry. We'd been talking about your CoV work in Asia even before the news from Wuhan broke, and he's been interested in meeting you. Would you mind if he joined our call this afternoon as well? Seems like a good opportunity to make the introduction, but we can do it another time if you'd rather just speak with me.

Erik

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 4:24 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Look forward to talking with you tomorrow Erik...

Cheers,

Peter

Peter Daszak
President

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New York, NY 10001

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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Tuesday, January 7, 2020 2:54 PM
To: Alison Andre; Peter Daszak
Subject: RE: Wuhan Pneumonia

Sure, that's perfect. He can reach me at

Thanks!
Erik

From: Alison Andre <andre@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 2:52 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Peter Daszak <daszak@ecohealthalliance.org>
Subject: Re: Wuhan Pneumonia

Hi Erik,

Can Peter give you a call around 3:30 tomorrow? If that works for you, please let me know the best number to reach you on.

Thanks!
Alison

From: "Stemmy, Erik (NIH/NIAID) [E]" <erik.stemmy@nih.gov>
Date: Tuesday, January 7, 2020 at 2:49 PM
To: Peter Daszak <daszak@ecohealthalliance.org>
Cc: Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

That would be great! Thank you for getting back to me. I wasn't sure if you were traveling or not, so I'd also reached out to Aleksei. I can be pretty flexible tomorrow, so just let me know what time works for you.

Very much appreciate your time!
Erik

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, January 7, 2020 2:48 PM
To: Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>
Cc: Alison Andre <andre@ecohealthalliance.org>
Subject: RE: Wuhan Pneumonia

Definitely focusing attention on this Erik – I spent New Year's Eve talking with our China contacts, and with ProMED staff between glasses!

I've got more information, but it's all off the record. Could I give you a call tomorrow to fill you in? I've cc'd Alison Andre who can arrange a time that works for a quick call….

Cheers,

Peter

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President

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New York, NY 10001

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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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promote conservation.

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:erik.stemmy@nih.gov]
Sent: Monday, January 6, 2020 7:28 AM
To: Peter Daszak
Subject: Wuhan Pneumonia

Hi Peter,
Happy New Year! I'm sure you've been following along with the Wuhan pneumonia cases, and I wanted to see if you had any information from your contacts over there. I saw SARS and MERS had been ruled out, but curious to know if there's any indication you've seen that another bat CoV might be involved.

Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone:
Email: erik.stemmy@nih.gov

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.
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To: Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; linfa.wang@duke-nus.edu.sg[linfa.wang@duke-nus.edu.sg]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]
Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: William Dowling[william.dowling@cepi.net]
Sent: Thur 1/23/2020 4:40:21 PM (UTC-05:00)
Subject: WHO Consultation regarding the Wuhan coronavirus
Letko_2020_receptor usage of 2019 nCoV.pdf
Zhao et al 2020 supp data.pdf
Zhou et al 2020.pdf

Hello all,

On behalf of the WHO R&D Blueprint team, I am writing to request your participation on a call tomorrow at 9 PM Central European time (which will be Saturday morning for some of you). The purpose of the call is to lend your expertise to coordination of WHO response efforts. To that end , we would like to discuss the current status of efforts to culture the Wuhan coronavirus (or generate a recombinant virus); recent sequence data and modeling of the Spike protein; and potential next steps to assess cross reactivity with other coronaviruses. We realize that this is very short notice, but the situation is very dynamic. This would be an initial call with lengthier and more detailed calls in the near future.

Also, for those who have not seen them, I am attaching two reports on this topic that just came out and are highly relevant to the conversation.

Please let us know if you can make it. Call in details will be sent tomorrow.

Thank you,

Bill Dowling (seconded to WHO)

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI New vaccines for a safer world

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(+1) (m)

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Functional assessment of cell entry and receptor usage for lineage B β-coronaviruses, including 2019-nCoV

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Abstract

Over the past 20 years, several coronaviruses have crossed the species barrier into humans, causing outbreaks of severe, and often fatal, respiratory illness. Since SARS-CoV was first identified in animal markets, global viromics projects have discovered thousands of coronavirus sequences in diverse animals and geographic regions. Unfortunately, there are few tools available to functionally test these novel viruses for their ability to infect humans, which has severely hampered efforts to predict the next zoonotic viral outbreak. Here we developed an approach to rapidly screen lineage B betacoronaviruses, such as SARS-CoV and the recent 2019-nCoV, for receptor usage and their ability to infect cell types from different species. We show that host protease processing during viral entry is a significant barrier for several lineage B viruses and that bypassing this barrier allows several lineage B viruses to enter human cells through an unknown receptor. We also demonstrate how different lineage B viruses can recombine to gain entry into human cells and confirm that human ACE2 is the receptor for the recently emerging 2019-nCoV.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) first emerged in humans in 2003 after transmitting from animals in open air markets in China[1,2]. Shortly thereafter, several genetically related viruses were identified in Chinese Horseshoes bats (*Rhinolophus sinicus*)[3-7]. At the same time, improvements in next generation sequencing technology lead to a boom of virus discovery, uncovering thousands of novel virus sequences in wild animal populations around the world. While most of these viruses have never been found in humans, many are genetically similar to known human viruses within the betacoronaviruses (β-CoV) genus. The β-CoVs are further divided into four lineages: lineage B, which includes SARS-CoV and the newly emerging 2019-nCoV, has approximately 200 published virus sequences whereas lineage C, which includes MERS-CoV, has over 500 viral sequences.

Every year, additional novel CoV sequences are discovered. However, there is a massive knowledge gap in the field as very little work is performed after the viral sequences are published. Therefore, it is unknown whether these novel viruses have the potential to emerge in human populations.

Current methods for studying novel β-CoVs are technically demanding. Viral isolation from field samples is rarely successful and reverse genetics recovery of recombinant virus is labor-intensive, and expensive as synthesis of a single genome can cost upwards of $15,000. These limitations are prohibitive to studying novel CoVs at the scale in which they are discovered.

Cell entry is an essential component of cross-species transmission, especially for the β-CoVs. All CoVs encode a surface glycoprotein, spike, which binds to the host-cell

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receptor and mediates viral entry[8]. For β-CoVs, a single region of the spike protein called the receptor binding domain (RBD) mediates the interaction with the host cell receptor. After binding the receptor, a nearby host protease cleaves the spike, which releases the spike fusion peptide, facilitating virus entry[9-12]. Known host receptors for β-CoVs include angiotensin converting enzyme 2 (ACE2) for SARS-CoV and dipeptidyl peptidase 4 (DPP4) for MERS-CoV[13,14].

Structural studies of coronaviruses have shown that the spike RBD is capable of folding independently from the rest of the spike protein and contains all of the structural information for host receptor binding[15]. Additionally, a previous study showed that replacing the RBD of the lineage B bat virus, Rp3, allowed the virus to enter cells expressing human ACE2 (hACE2)[16]. We therefore developed a method to functionally test the RBDs from novel lineage B β-CoVs in place of the SARS-CoV spike RBD (figure 1). Synthesizing just the RBD of spike is much faster and cost-effective than conventional pseudotyping methods that rely on synthesis of the full ~4kb spike sequence for novel CoVs: a process that can take weeks and is cost-prohibitive for large panels of spike sequences. The short turnaround time for our approach allowed us to test the receptor usage of all published, unique RBD sequences in lineage B, and also rapidly confirm the ACE2 receptor usage of the 2019-nCoV spike, which emerged in China in January 2020 as our study was ongoing.

We show that lineage B RBDs divide into functionally distinct clades and that several previously-unappreciated viruses exhibit compatibility with an unknown receptor on human cells. We also show that these clades are capable of recombining to impart human host-cell entry phenotypes, and that, beyond the RDB-receptor interaction, host

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protease processing is another species barrier encountered by lineage B β-CoVs during cell entry.

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Methods

Cells

293T, A549, BHK, Caco-2, Huh-7.5, PK-15, and Vero cells were maintained in DMEM (Sigma) supplemented with 10% FBS, penicillin/streptomycin, and L-glutamine. RhiNi/40.1, AJ-primary, AJ*i*, HypNi, RaKSM-2.5i, RhiLu, and RhiNi cells were maintained in DMEM/F12 (Gibco) supplemented with 12% FBS, penicillin/streptomycin, non-essential amino acids, sodium pyruvate and L-glutamine. AJ-primary cells were immortalized with a lentiviral vector expressing SV40 T-antigen following the manufacturer's instructions to generate AJ*i* cells (abm; #G203). RaKSM-2.5 primary cells have been previously described and were immortalized in this study similar to AJ*i* cells[17].

Plasmids

The spike coding sequences for SARS-CoV Urbani, As6526, and BM48-31 were codon optimized for human cells, appended with a 5' kozak expression sequence (GCCACC) and 3' tetra-glycine linker followed by nucleotides encoding a FLAG tag sequence (DYKDDDDK). For SARS-CoV spike, silent mutations were introduced around codons 308 and 519 to form KpnI and XhoI digest sites. For As6526 spike, silent mutations were introduced around codons 290 and 501 to form AflII and HindIII digest sites. For BM48-31 spike, silent mutations were introduced around codons 295 and 501 to form AflII and HindIII digest sites. These engineered spike sequences were synthesized and cloned into pcDNA3.1+ (GenScript).

Spike RBDs were first codon-optimized for human cells, appended with regions of the target spike backbone to facilitate Infusion cloning and synthesized as double

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stranded DNA fragments (IDT DNA). SARS-CoV, As6526 or BM48-31 engineered spike plasmids were digested with their corresponding restriction enzymes and gel purified. RBD inserts were resuspended in water and Infusion cloned into gel purified, digested spike backbone vectors (Takara).

Human ACE2 (Q9BYF1.2), DPP4 (XM_005246371.3), or APN (NP_001141.2) were synthesized and cloned into pcDNA3.1+ (GenScript). All DNA constructs were verified by Sanger sequencing (ACGT Inc.).

Receptor transfection

BHK cells were seeded in black 96-well plates and transfected the next day with 100ng plasmid DNA encoding human ACE2, DPP4, APN or empty vector, using polyethyleneimine (Polysciences). All downstream experiments were performed 24 hours post-transfection.

Pseudotype production

Pseudotypes were produced as previously described[18]. 293T cells were seeded onto 6-well plates pre-coated with poly-L-lysine (Sigma) and transfected the next day with 1200ng empty plasmid and 400ng of plasmid encoding coronavirus spike or GFP as a no pseudotype control. Twenty-four hours later, transfected cells were infected with VSVΔG particles pseudotyped with VSV-g as previously described[19]. After one hour of incubating at 37°C, cells were washed three times and incubated in 2mL DMEM supplemented with 2% FBS, penicillin/streptomycin, and L-glutamine for 48 hours. Supernatants were collected, centrifuged at 500xG for 5 minutes, aliquoted and stored at -80.

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Luciferase-based cell entry assay

Target cells were seeded in black 96-well plates and inoculated, in triplicate, with equivalent volumes of pseudotype stocks. For trypsin experiments, pseudotype stocks were diluted 1:1 in DMEM without FBS, trypsin was added to a final concentration of 2500μg/mL and samples were incubated at 37°C for 15 minutes. Samples were then diluted again 1:1 in cold DMEM supplemented with 2% FBS and added to cells. Inoculated plates were centrifuged at 1200xG, 4°C, for 1 hour and incubated over night at 37°C. Approximately 18-20 hours post-infection, Bright-Glo luciferase reagent (Promega) was added to each well, 1:1, without removing culture media and luciferase was measured. Relative entry was calculated by normalizing the relative light unit (RLU) for spike pseudotypes to the plate RLU average for the "no pseudotype control."

Western blot

Producer cells (spike-transfected 293T) were lysed in 1%SDS, 150mM NaCl, 50mM Tris-HCl, 5mM EDTA and clarified by centrifugation at 14000xG for 20 minutes. Pseudotyped particles were concentrated from producer cell lysates that were overlaid a 10% OptiPrep cushion in PBS (Sigma) and centrifuged at 20,000× g for 2 hours at 4 °C. Lysates and concentrated particles were analyzed for FLAG, GAPDH and/or VSV-m expression on 10% Bis-Tris PAGE gel (ThermoFisher).

Accession numbers

Accession numbers for all spike sequences used here can be found in figure s1b.

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Results

ACE2 entry is lineage B clade 1-specific

The receptor binding domain (RBD) of lineage B β-CoVs is a single, continuous domain that contains all structural information necessary to interact with the host receptor (figure 1a, b). We introduced silent mutations in the codon optimized coding sequence for SARS-CoV to facilitate replacing the SARS RBD with the RBD from other lineage B viruses (figure 1b). All lineage B sequences were downloaded from online repositories and parsed to 29 unique RBD sequences, representing all published variations of the lineage B RBD (supp. fig 1a, b). The panel of 29 RBDs phylogenetically cluster into 3 clades, as previously described[5], but these RBD clades were not apparent in phylogenetic analysis of other viral sequences, such as the RNA-dependent RNA polymerase (supp. fig 1c). All 29 RBDs were codon optimized, synthesized and cloned in place of the SARS RBD, effectively generating chimeric spike expression constructs. We then generated VSV-luciferase reporter particles pseudotyped with the chimeric spikes (figure 1c). We chose VSV over lentiviruses as our pseudotype platform because a lentiviral pseudotypes have failed to accurately reflect viral entry with novel bat coronavirus spike protein[7]. All constructs exhibited similar levels of expression in producer cells and incorporation into VSV pseudotypes, except the chimera with BM48-31 which displayed somewhat reduced expression compared to WT SARS spike (figure 1d). We then infected BHK cells expressing the receptor for SARS-CoV or empty vector (figure 1e) and observed only clade 1, which includes SARS-CoV, WIV1 and SHC014, could enter cells transfected with human ACE2 (figure 1e).

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Protease enhances clade 2 entry

After binding the host receptor, host-cell protease cleaves spike, releasing the fusion peptide and allowing for host cell entry [20]. Previous studies have shown that absence of the host protease or incompatibility between the host protease and viral spike can block viral entry [21-24]. To circumvent host-cell protease incompatibility or absence, we treated our lineage B pseudotype panel and infected a wide variety of cell types from different host species (figure 2, supp. fig. 2). In the absence of exogenous protease, only clade 1 infected cells from African green monkey kidney, human gastrointestinal tract, human liver, and porcine kidney, in agreement with previous studies (figure 2; supp. fig. 2a, b). Surprisingly, exogenous protease enhanced entry of a subset of clade 2 spike chimeras in nonhuman primate, bat and human cells (figure 2). Importantly, VSV-g pseudotyped particles were able to produce luciferase signal in all cell lines tested in this study (supp. fig. 2c).

Clade 2 entry is receptor-dependent

We next tested human variants of known β-CoV receptors for their ability to mediate cell entry of clade 2 and 3 spike chimeras. We also tested human aminopeptidase N (APN), a receptor for alphacoronaviruses, which have been shown to utilize either human ACE2 or human APN for cell entry (figure 3a). Protease treatment only enhanced entry of clade 1 RBDs on cells expressing human ACE2, but not human DPP4 or APN. No entry was observed with clade 2 or 3 spikes, regardless of receptor or protease addition. Human dipeptidyl peptidase IV (DPP4), the receptor for the lineage C β-CoVs, MERS-CoV, only mediated entry of MERS-CoV (figure 2b, middle panels).

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Importantly, in the absence of receptor, no entry was observed for any of the pseudotypes, suggesting that protease-mediated entry is receptor-dependent (figure 2b, right panels).

Receptor usage of 2019-nCoV

While our study was ongoing, a novel lineage B virus tentatively named 2019-nCoV was identified as the cause of a pneumonia outbreak in Hubei, China. Once the sequence was publicly available, we synthesized, cloned and tested the RBD from 2019-nCoV in our assay with human variants of known coronavirus receptors. The chimeric SARS-2019-nCoV spike protein expressed and was incorporated into particles similarly to other clade 1 chimeric spikes (figure 3c). The 2019-nCoV RBD was capable of entering cells expressing human ACE2, but not any of the other receptors tested (figure 3d; s3).

Clade determinants for ACE2 usage

Consensus sequences of the three lineage B clades showed several key differences between these groups. Only clade 1 RBDs contain all 14 residues that have been shown through crystallography, to interact with human ACE2 (figure 4a; s4). The majority of these residues are absent from clades 2 and 3, which contain additional deletions in surface exposed loops that cluster at the interface with ACE2 (figure 4 a, b). We generated a series of clade consensus RBD variants to determine the minimum number of mutations needed to impart ACE2 function on clade 2 and 3 RBDs (figure 4c). Introducing the two loop deletions from clade 1 in clade 2 results in a reduced spike expression, impaired pseudotype incorporation and loss of cell entry (figure 4c, d).

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Restoring these loops in clade 2 and 3 from the loops found in clade 1 did not enhance entry with ACE2 (figure 4c; 2→1 and 3→1 version 1). Introducing all 14 ACE2 contact points in clade 2 or 3 also failed to restore ACE2 entry (figure 4c; 2→1 and 3→1 version 2). Only replacing all 14 contact points and the surrounding amino acids (also known as the receptor binding motif, RBM) lead to increased ACE2 entry with clade 2 and 3 RBDs (figure 4c; 2→1 version 3 = clade 2 residues 322-400 + clade 1 residues 400-501; 3→1 version 3 = clade 3 residues 322-385 + clade 1 residues 386-501). Taken together, these results show that the entire RBM from clade 1 is needed for ACE2 entry.

Full-spike and RBD chimeras are comparable

We next synthesized full-length clade 2 and 3 spikes to compare to our RBD chimeras. We selected the clade 2 spike, As6526, because it consistently gave strong entry signal in human cells following protease-treatment (figure 2b) as well as BM48-31, the only clade 3 spike in our panel. As we did for SARS-CoV spike, clade 2 and 3 spikes were codon optimized, FLAG-tagged and silent mutations were introduced to facilitate replacing their RBD with the consensus RBD from clade 1 (figure 5a). All chimeric constructs expressed similarly, with the exception for the SARS-BM48-31 RBD chimera, which exhibited reduced expression and incorporation (figure 5b). Protease treatment enhanced entry of both the As6526 clade 2 RBD chimera and full-length spike entry into Huh cells (figure 5c). Protease treatment had no effect on either the BM48-31 clade 3 chimera or full-length spike (figure 5c). Taken together, these findings show that SARS-lineage B RBD chimeras reflect the entry phenotype of full-length lineage B spikes.

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Finally, we tested if receptor-binding and protease processing are coupled. We replaced the RBD of full-length clade 2 and 3 spike with the consensus RBD from clade 1 and tested pseudotypes on cells expressing the clade 1 receptor. The clade 1 consensus RBD efficiently facilitated entry of both As6526 and BM48-31 spike only following protease treatment. These findings show that even though BHK-hACE2 cells support full-length clade 1 spike entry, just having the RBD from a clade 1 virus is insufficient to mediate entry. As seen in our previous experiments, protease treatment did not enhance pseudotype entry in the absence of host receptor (figure 5).

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Discussion

Despite significant advances in next generation sequencing technologies, which have facilitated the discovery of thousands of novel animal-derived viruses, tools for downstream functional assessment of these novel sequences are lacking. To gain traction on this ever-growing problem, we took a reductionist approach to coronavirus entry and developed a scalable, BSL2-compatible method for testing only the minimal region of the virus essential for interacting with the host receptor (figure 1, figure s1a). Because most of these viruses have never been isolated, we resorted to synthetic biology and molecular engineering to reduce the burden of gene synthesis to just a small fragment. Thus, the cost and synthesis production time for testing several spikes for entry in our system is dramatically reduced (figure s1d). In theory, this approach to functional viromics should be applicable to a wide variety of virus-host proteins and interactions.

Coronavirus entry is a multi-step process involving multiple, distinct domains in spike that mediate virus attachment to the cell surface, receptor engagement, protease processing and membrane fusion[8]. While the RBD:receptor interaction is most studied in this process, recent studies have highlighted the major role host protease processing plays as a species barrier[22,25-27]. Lineage C coronaviruses include MERS-CoV as well as distantly related viruses such as HKU4, HKU5 and PDF-2180 [28,29]. Studies have shown that HKU4 can bind human DPP4 but requires addition of exogenous trypsin to facilitate cell entry and that HKU5 and PDF-2180 spikes can enter human cells through an unidentified receptor with protease treatment[22,26]. Analogous to these earlier studies of lineage C CoVs, we observed protease-enhanced entry of lineage B CoVs (figure 2, 3, 5). While it has been shown that host proteases cleave spike, allowing for downstream

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membrane fusion, other evidence suggests that protease may act on the receptor as well to activate it[30]. Addition of protease during the course of SARS-CoV infection facilitated entry in cells with low-expression of ACE2 that is normally insufficient to support virus entry[30]. Indeed, we saw evidence of residual trypsin activity on the cells after infection in our studies as the cell monolayer was loose compared to the untreated condition. Similarly, Menachery et al. also observed cell rounding during their trypsin infections[26]. Therefore, further studies are needed to assess where trypsin is enhancing entry of coronaviruses: at the level of spike, the receptor, or both.

In the absence of exogenous protease, only clade 1 RBDs entered nonhuman primate, human and porcine cell lines (figure 2a, b, s2a, b). These findings are in strong agreement with previous studies that have either isolated virus (WIV1) or rescued recombinant chimeric viruses (SHC014, Rs4231, Rs7237)[5,7,31]. However, with trypsin, a subset of genetically-similar clade 2 RBDs gained entry in these cells, suggesting their barrier is at the level of protease processing (figure 2a, b). The other spike from clade 2 and 3 did not enter the cells we tested, regardless of protease addition, suggesting an absent or incompatible receptor. Surprisingly, the protease-dependent entry phenotype was consistent in the reverse spike chimeras in which we replaced the RBD in clade 2 or 3 spike with a clade 1 RBD (figure 5d), suggesting that either the protease site between S1/S2 is not compatible with the chimeric spike backbone or the protease is not expressed in these cells (figure s5). Because clade 1 spikes enter cells expressing human ACE2 without addition of protease but clade2-clade1 chimeras require protease, our data suggests the spike protease cleavage site is adapted to the protease environment of the receptor-bound RBD (figure s5).

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None of the spike pseudotypes efficiently entered *Rhinolophus* cells, which has been observed in previous studies using these cells[32,33] (figure 2c). Surprisingly, AJi cells were selectively permissive for only clade 2 entry following protease treatment, which suggests that clade 2 RBDs interact with a receptor that is distinct from clade 1 (figure 2c).

Our results show that, despite all being classified as the same virus species, most lineage B β-CoVs do not use currently known coronavirus receptors (figure 1e, 3a, b). Critically, we did not observe any pseudotype entry in the presence of protease and absence of receptor, suggesting that lineage B cell entry is still receptor-dependent following protease treatment (figure 3b). While our study was ongoing, a novel lineage B β-CoV was identified as the etiological agent behind an outbreak of pneumonia in Wuhan, Hubei, China (2019-nCoV). The RBD for 2019-nCoV has residues and motifs found in all 3 clades but forms a distinct clade, so we tested it for receptor usage and observed entry only with human ACE2 but not other known coronavirus receptors (figure 3d). Interestingly, within the backbone of SARS-CoV spike, cell entry of 2019-nCoV was similar to the other clade 1 spikes tested, including SARS-CoV. These finding suggests 2019-nCoV is capable of using human ACE2 as efficiently as SARS-CoV, which may help explain the human-to-human transmissibility of this virus. More studies are needed with the full spike sequence and, ideally, a viral isolate.

The receptor binding motif (RBM) is a small region in the C-terminal half of the RBD and contains all the residues that interface with the host receptor (figure 3a)[15]. The 14 contact points in the co-structure of the SARS-RBD bound to human ACE2 are largely absent from clade 2 and 3 RBDs, which also contain deletions compared to clade 1 RBMs (figure 4a, b, s4a). Simply mutating clade 2 and 3 to have the 14 contact points was

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insufficient to impart human ACE2 usage (figure 4c). This is likely because the non-contact residues in the RBM play a supportive and structural role for these contact points, and indeed, these non-contact residues are different between the clades (figure s4).

In contrast to changing individual amino acids, our chimeric RBD constructs show that clade 2 and 3 RBD containing the clade 1 RBM are compatible with human ACE2. Coronaviruses frequently undergo recombination, gaining large swaths of genetic material at once [34,35]. Taken together with our data, it is possible that recombination with a clade 1 virus will impart compatibility with human ACE2. Interestingly, the 2019-nCoV RBD forms a clade that is distinct from the other 3 clades (figure s1c). However, the 2019-nCoV RBD contains most of the contact points with human ACE2 that are found in clade 1 as well as some amino acid variations that are unique to clade 2 and 3 (figure s4b). Taken together with our receptor assay results, it may be possible that 2019-nCoV arose from recombination between clade 1 and the other clades.

As we saw with the SARS-As6526 RBD (clade 2) spike chimera, full length As6526 spike entered cells following protease treatment, but BM48-31 (clade 3) spike did not (figure 2, 5c). These data show that the chimeric spikes generally reproduce the entry phenotypes of full-length spikes. Notably, the full length As6526 spike did not enter cells as efficiently as the SARS-As6526 chimera, suggesting that other human-cell adaptations are likely needed in As6526 spike.

The capacity to predict the zoonotic potential of newly detected viruses has been severely hindered by a lack of functional data for these novel animal virus sequences. Here, we have developed a rapid and cost-effective platform to functionally test large groups of related viruses for zoonotic potential. We found that several other lineage B

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coronaviruses are capable of entering human cells through an unknown receptor and that lineage B spike proteins can recombine to gain entry with a known host-receptor. Taken together with the latest outbreak of 2019-nCoV in humans, these findings underscore the importance of continued surveillance of coronaviruses at the sequence and functional levels in order to better prepare for the next emerging virus.

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Declarations of Interests

The authors declare no competing interests.

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Figures

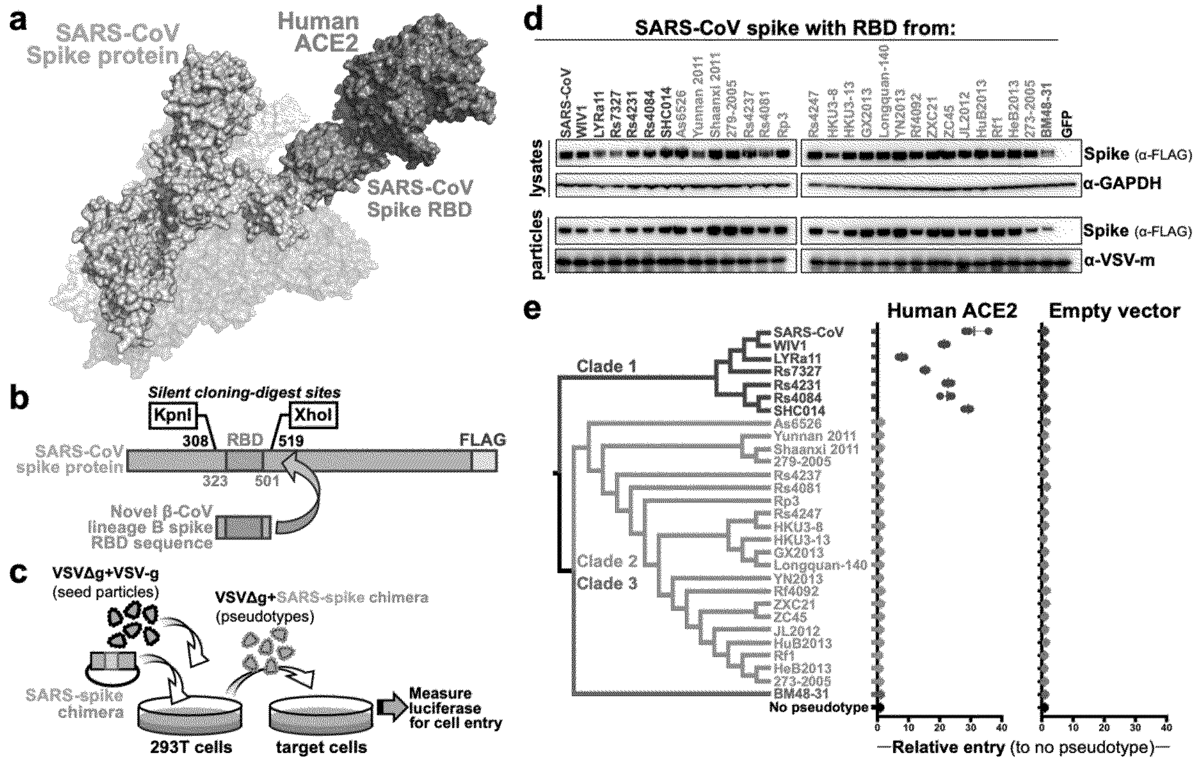

Figure 1: β-Coronavirus lineage B entry with human ACE2 is clade-specific

a, β-Coronaviruses, including SARS-CoV, interact with the host cell receptor via the Receptor Binding Domain (RBD) in spike (PDB: 5X5B, 2AJF) . **b,** SARS-CoV spike was engineered with silent mutations to facilitate cloning novel RBD sequences in place of the SARS spike RBD. SARS spike amino acid numbers are indicated for silent cloning sites and the RBD in grey and orange, respectively. **c,** outline of experimental workflow. **d,** Westernblot of producer cell lysates and concentrated reporter particles. **e,** BHK cells were transfected with either human ACE2 or empty vector, subsequently infected with VSV-reporter particles pseudotyped with chimeric spikes, luciferase was measured and normalized to no pseudotype as a readout for cell entry. Shown are the data for 3 replicates.

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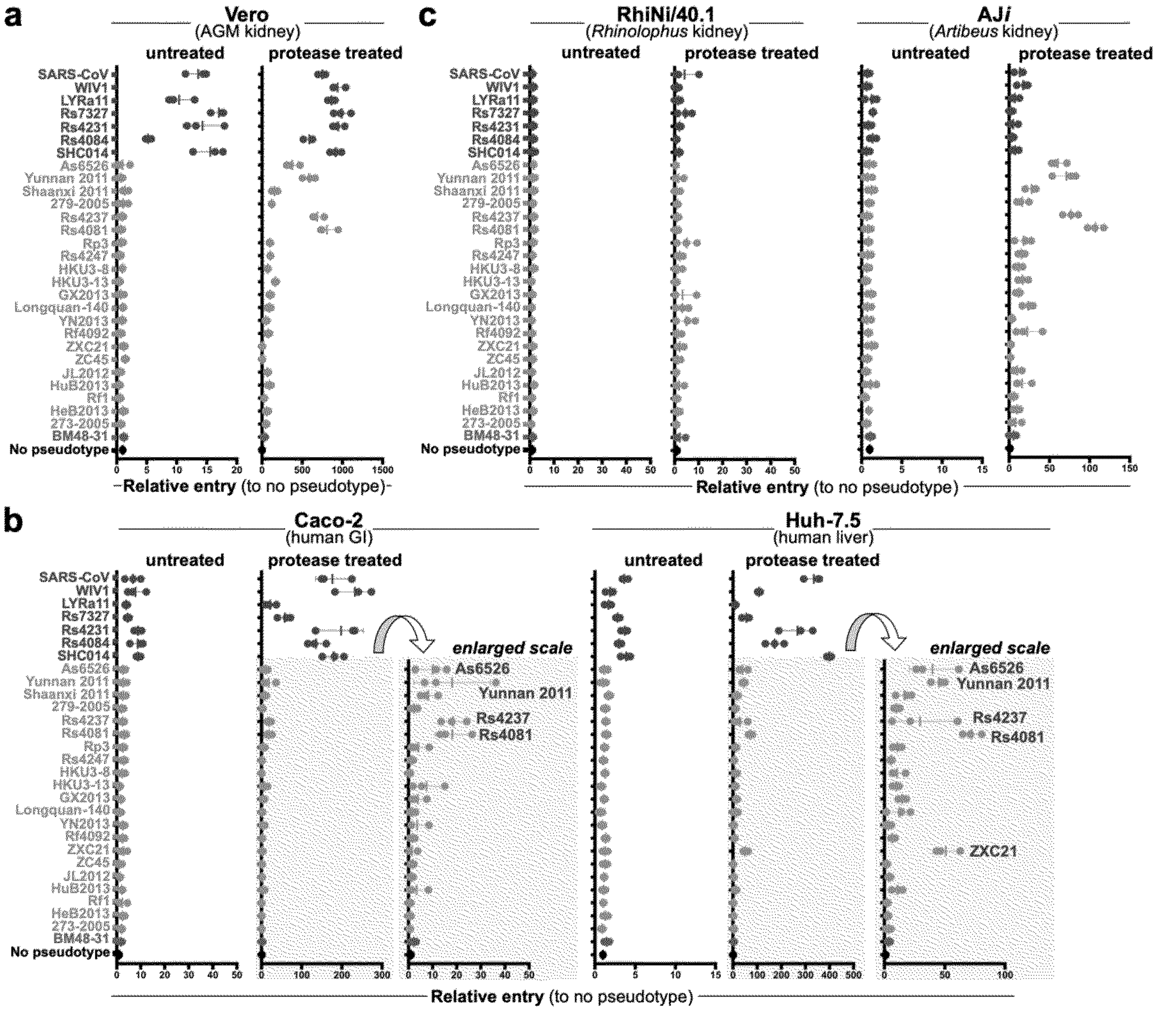

Figure 2: Trypsin enhances lineage B entry in various cell lines

a, Primate cells, **b,** human cells or **c,** bat cells were infected with VSV-particles pseudotyped with the lineage B chimeric spike panel. Pseudotypes were either left untreated or incubated with trypsin before addition to the cells. Luciferase was measured and normalized to particles produced without pseudotype. Shown are the data for 3 replicates.

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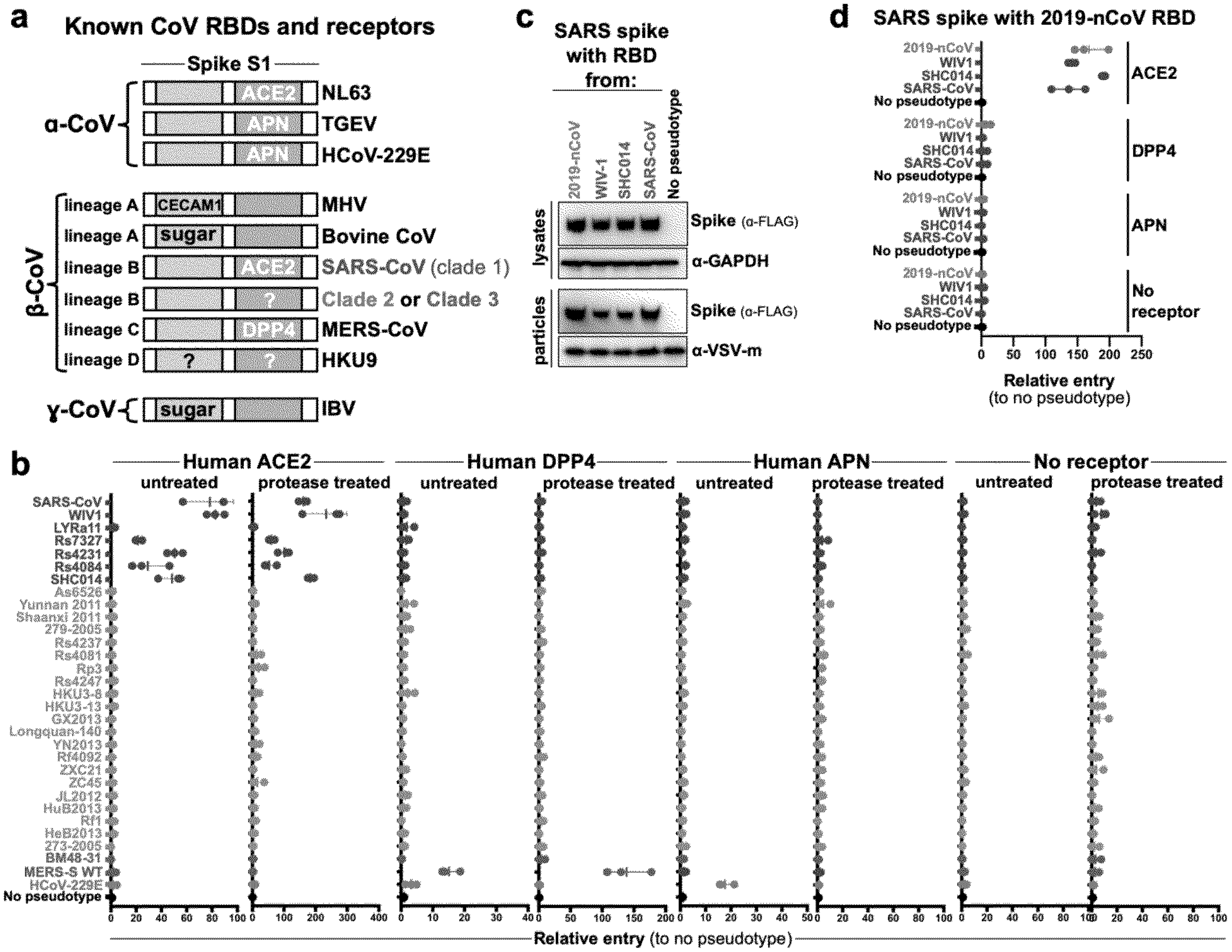

Figure 3: Lineage B entry into cells with known CoV receptors

a, Schematic of known coronavirus RBDs and their receptors. **b,** Pseudotyped particles were either left untreated and treated with trypsin and subsequently used to infect BHK cells transfected with the coronavirus receptor indicated. Shown are data from 3 replicates. **c,** Expression and pseudotype incorporation of SARS-S-2019-nCoV RBD chimeras. **d,** Pseudotypes were used to infect cells expressing hACE2, hDPP4, hAPN, or empty vector, without protease treatment.

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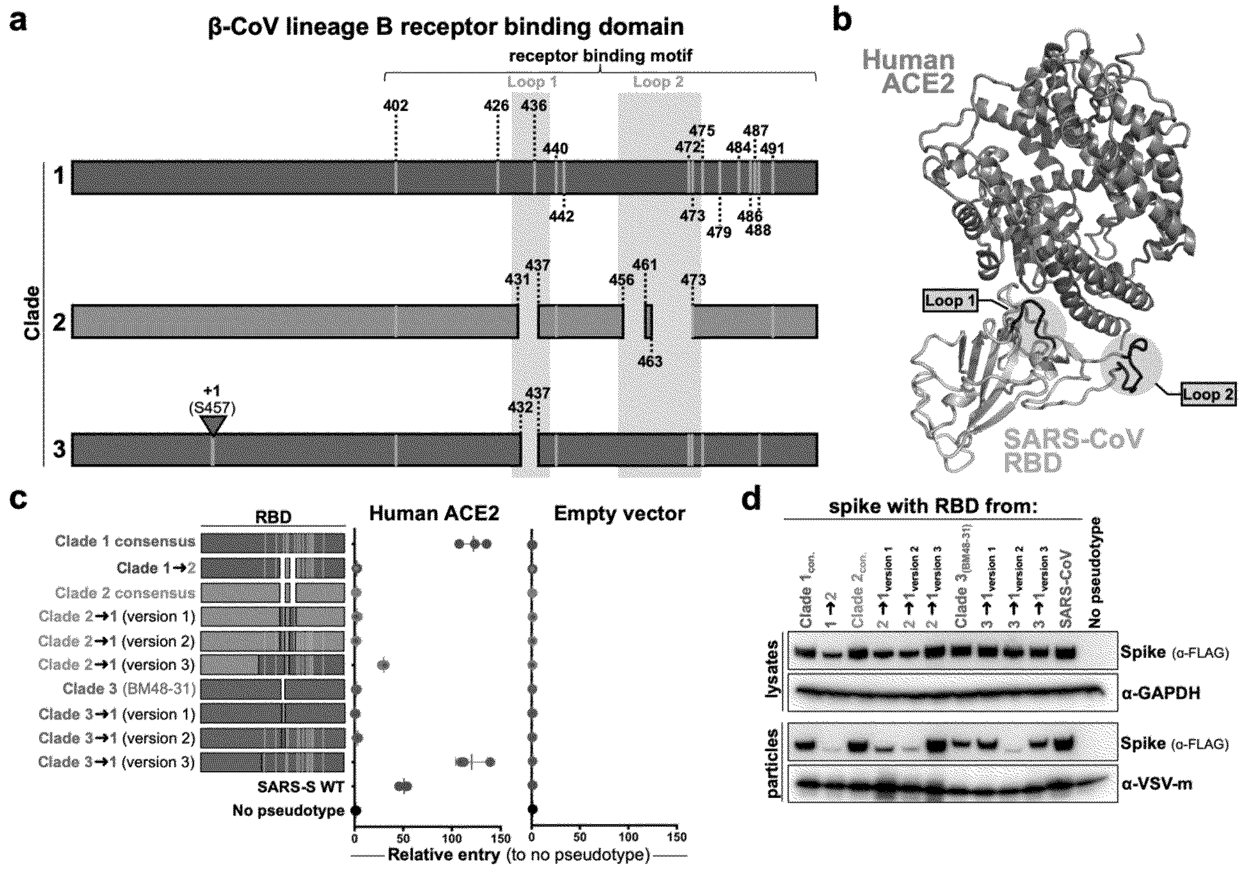

Figure 4: Lineage B clade-specific determinants for human ACE2 usage

a, Schematic overview of clade 1, 2 and 3. Highlighted in yellow are the 14 residues that contact human ACE2. Deletions in loops 1 and 2 are indicated for clades 2 and 3. **b,** Structure of human ACE2 and the SARS-S RBD (PDB: 2AJF), with loops highlighted in gray. **c,** VSV pseudotypes were generated with the indicated RBD and used to infect BHKs transfected with either human ACE2 or empty vector. Shown are data for 3 replicates. **d,** Westernblot of producer cell lysates and concentrated pseudotyped particles.

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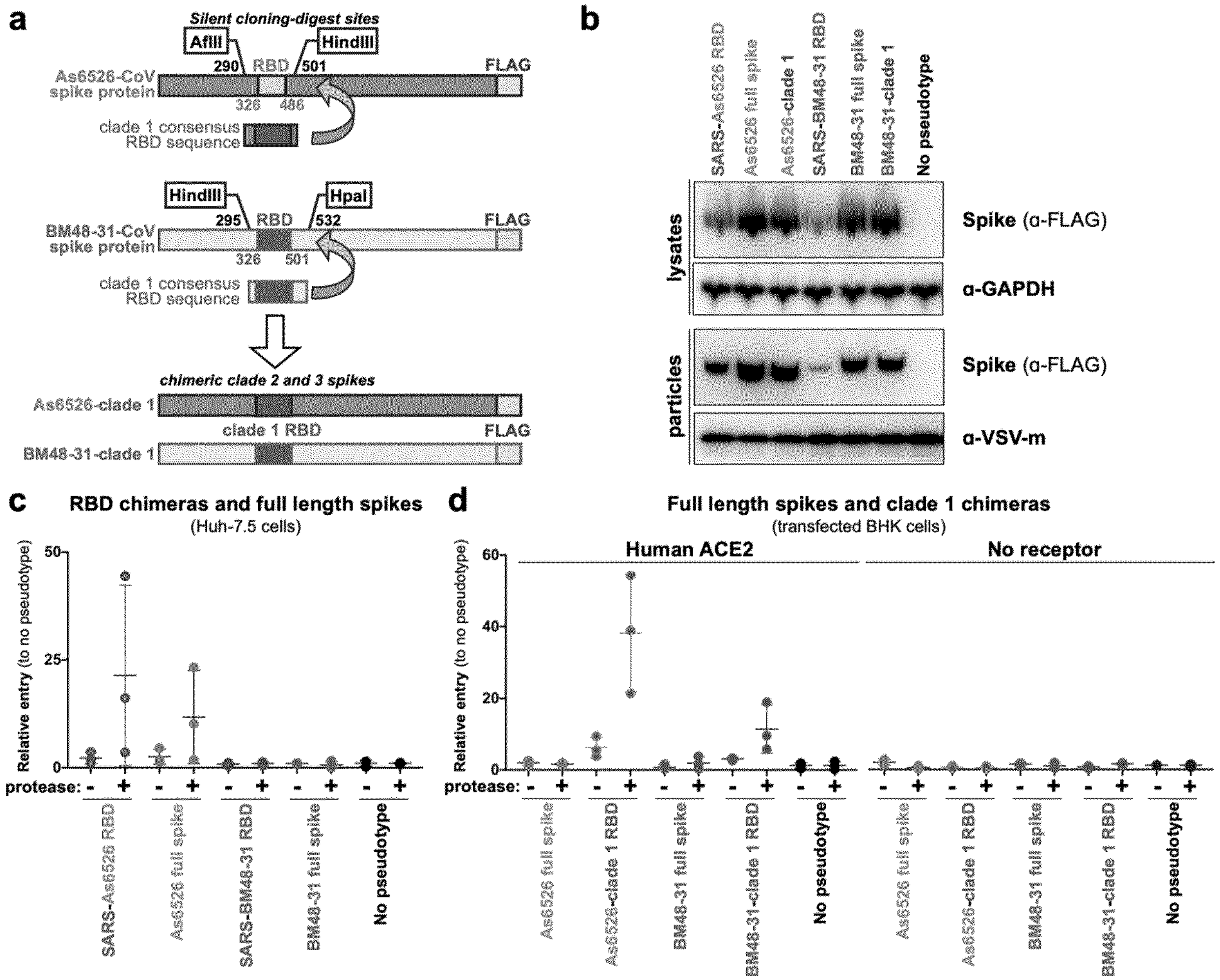

Figure 5: Comparison of chimeric and full-length clade 2 and 3 spikes

a, Full length spike sequences from As6526 (clade 2) and BM48-31 (clade 3) were codon optimized, FLAG tagged and synthesized. Silent mutations flanking the RBD facilitated replacing the native RBD with the clade 1 consensus RBD. **b,** Westernblot of producer cell lysates and concentrated pseudotypes particles. **c,** Pseudotypes with indicated spike constructs were left untreated or treated with trypsin and subsequently used to infect Huh-7.5 cells. Shown are data for 3 replicates. **d,** Pseudotypes with indicated spike constructs were left untreated or treated with trypsin and subsequently used to infect BHK cells transfected with human ACE2. Shown are data for 3 replicates.

Supplementary materials

Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin

Peng Zhou[1]*, Xing-Lou Yang[1]*, Xian-Guang Wang[2]*, Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin[4] Liu, Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1], Zheng-Li Shi[1]†

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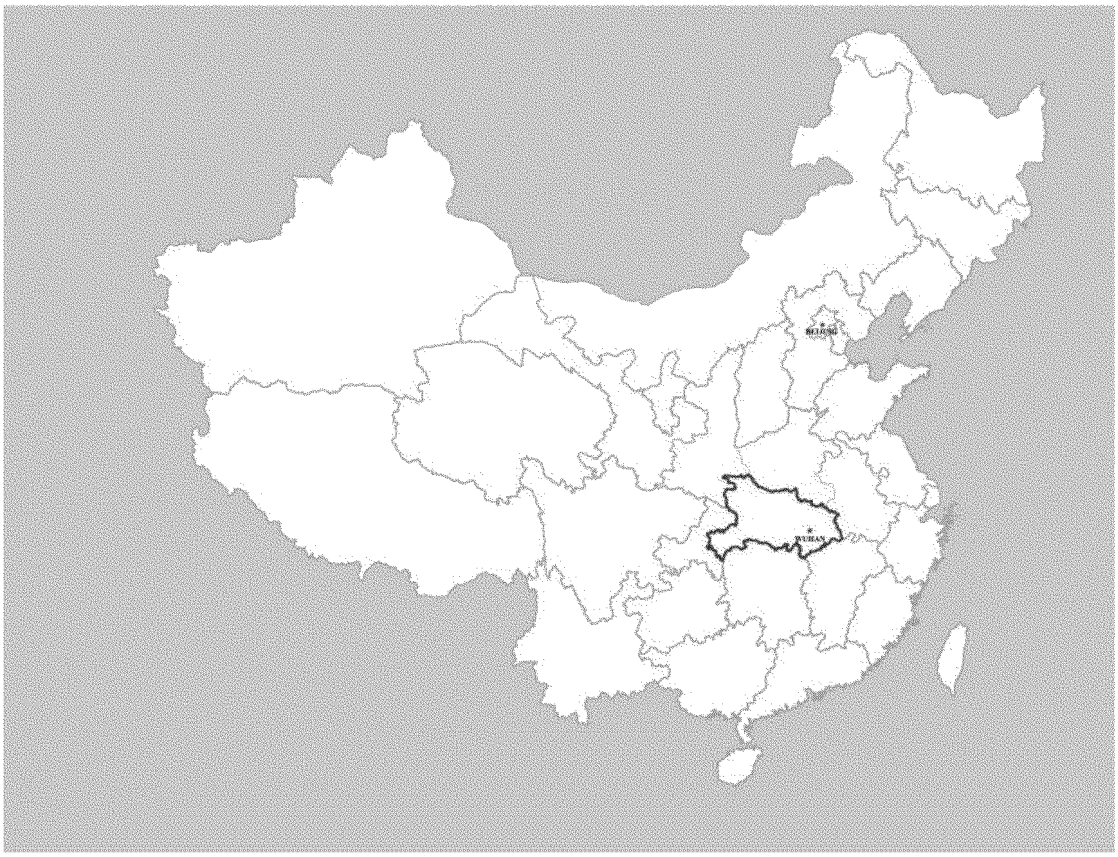
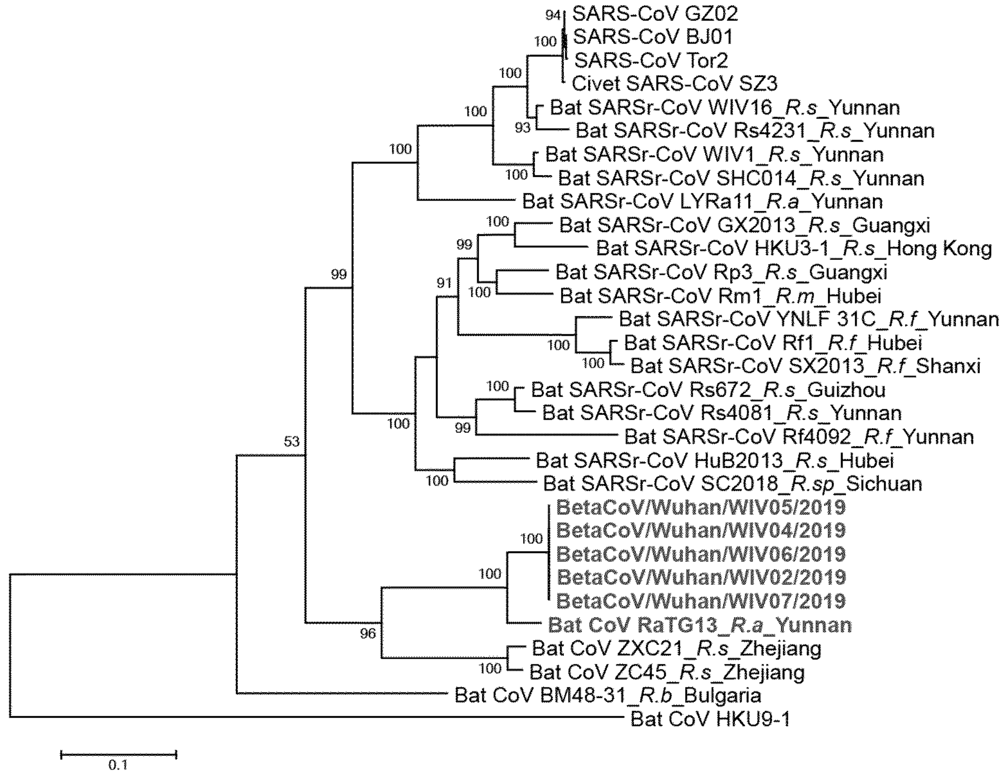
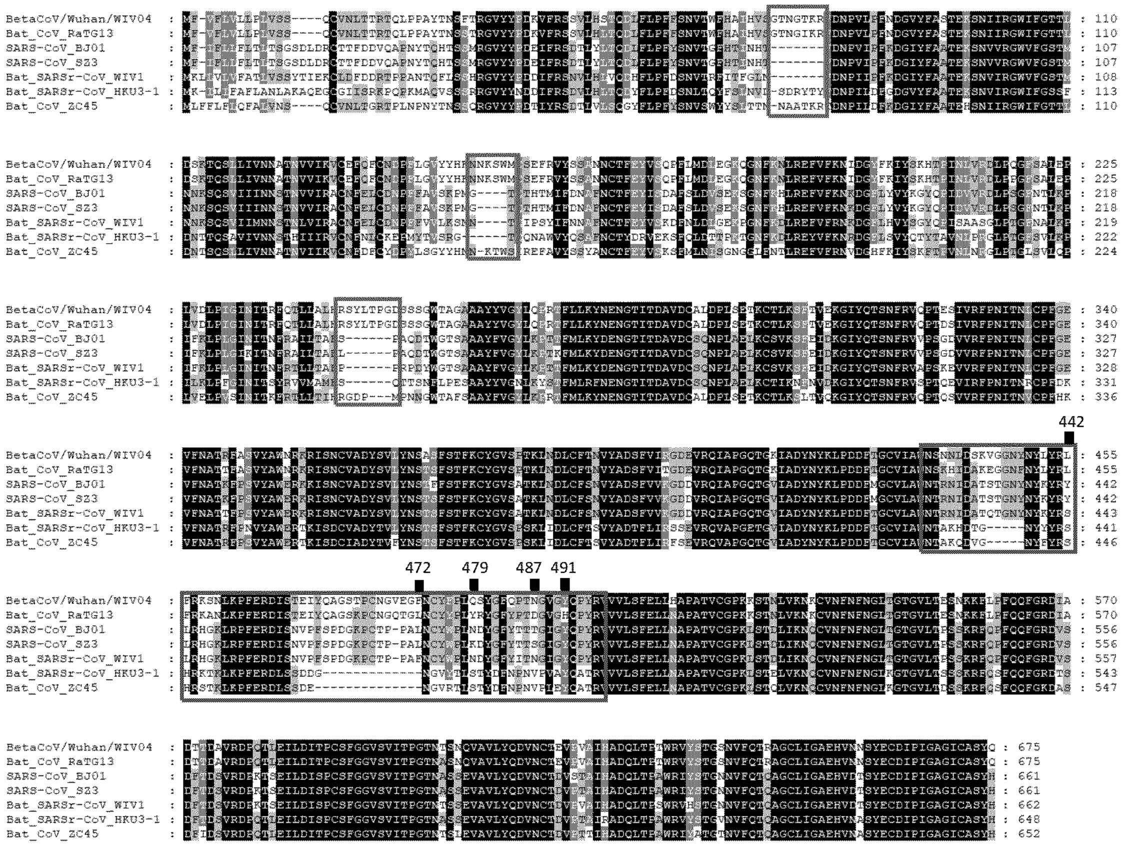
Extended Data Fig. 1 | Map of Wuhan. Wuhan, located in central China Hubei province (circled), has more than 11 million citizens.



Extended Data Fig. 2 | Phylogenetic tree base on the complete S gene sequence. nCoV-2019 and bat CoV RaTG13 are in bold. R.s, *Rhinolophus sinicus*; R.a, *Rhinolophus affinis*; R.f, *Rhinolophus ferrumequinum*; R.m, *Rhinolophus macrotis*; R.b, *Rhinolophus blasii*. Bat CoV HKU9-1 was used as outgroup. The trees were constructed by the maximum likelihood method using the Jukes-Cantor model with bootstrap values determined by 1000 replicates. Bootstraps > 50% are shown.

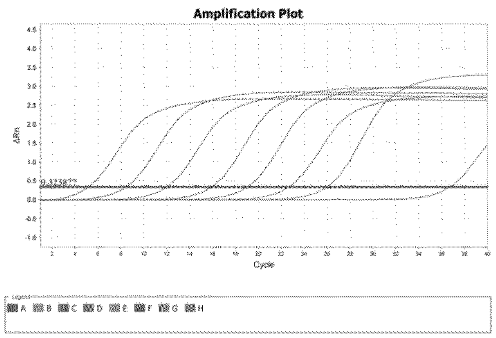


Extended Data Fig. 3 | Amino acid sequence alignment of the S1 protein of the nCoV-2019 with SARS-CoV and selected bat SARSr-CoVs. The receptor-binding motif of SARS-CoV and the homologous region of other coronaviruses are indicated by the red box. The key amino acid residues involved in the interaction with human ACE2 are numbered on top of the aligned sequences. The short insertions in the N-terminal domain of the novel coronavirus are indicated by the blue boxes. Bat CoV RaTG13 was identified from *R. affinis* in Yunnan Province. Bat CoV ZC45 was identified from *R. sinicus* in Zhejiang Province.

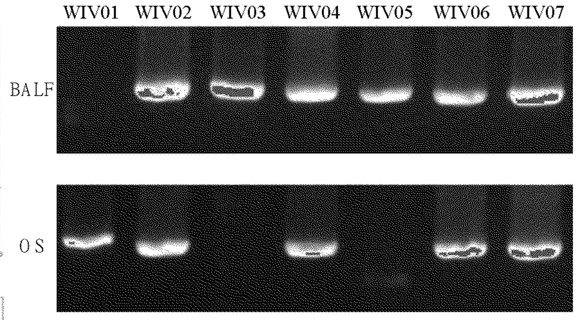


Extended Data Fig. 4 | Molecular detection method set up for nCoV-2019. **a**, molecular detection using conventional PCR. Primer sequence can be found in material and methods. **b**, standard curve for qPCR primers. PCR product of spike gene that was serial diluted to 10^8 to 10^1 (from left to right) was used as template. Primer sequence and experiment condition can be found in material and methods. **c**, specificity of qPCR primers. Nucleotide samples from the indicated pathogens were used.

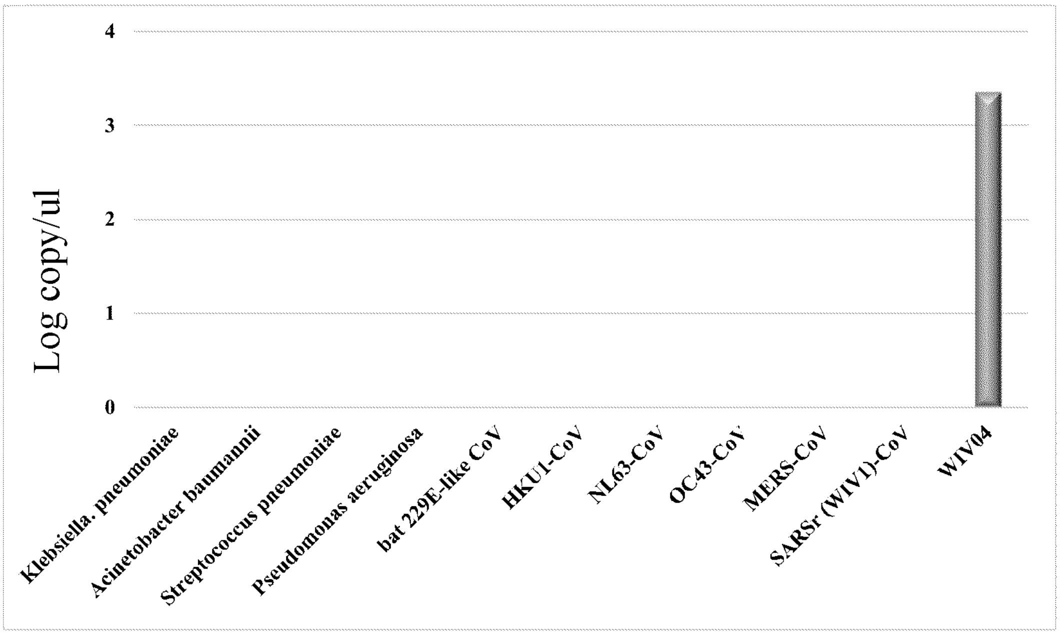
a



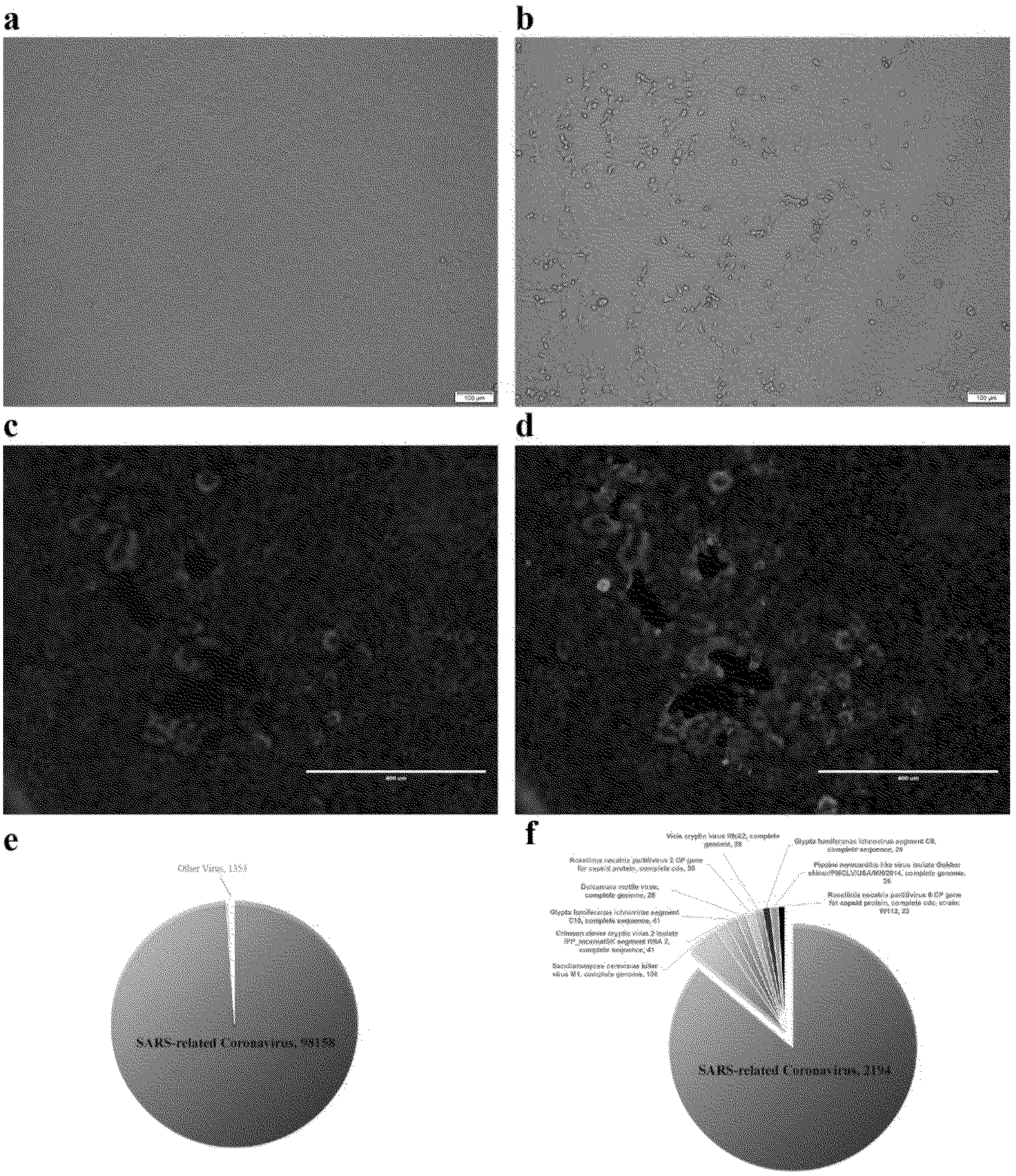
c



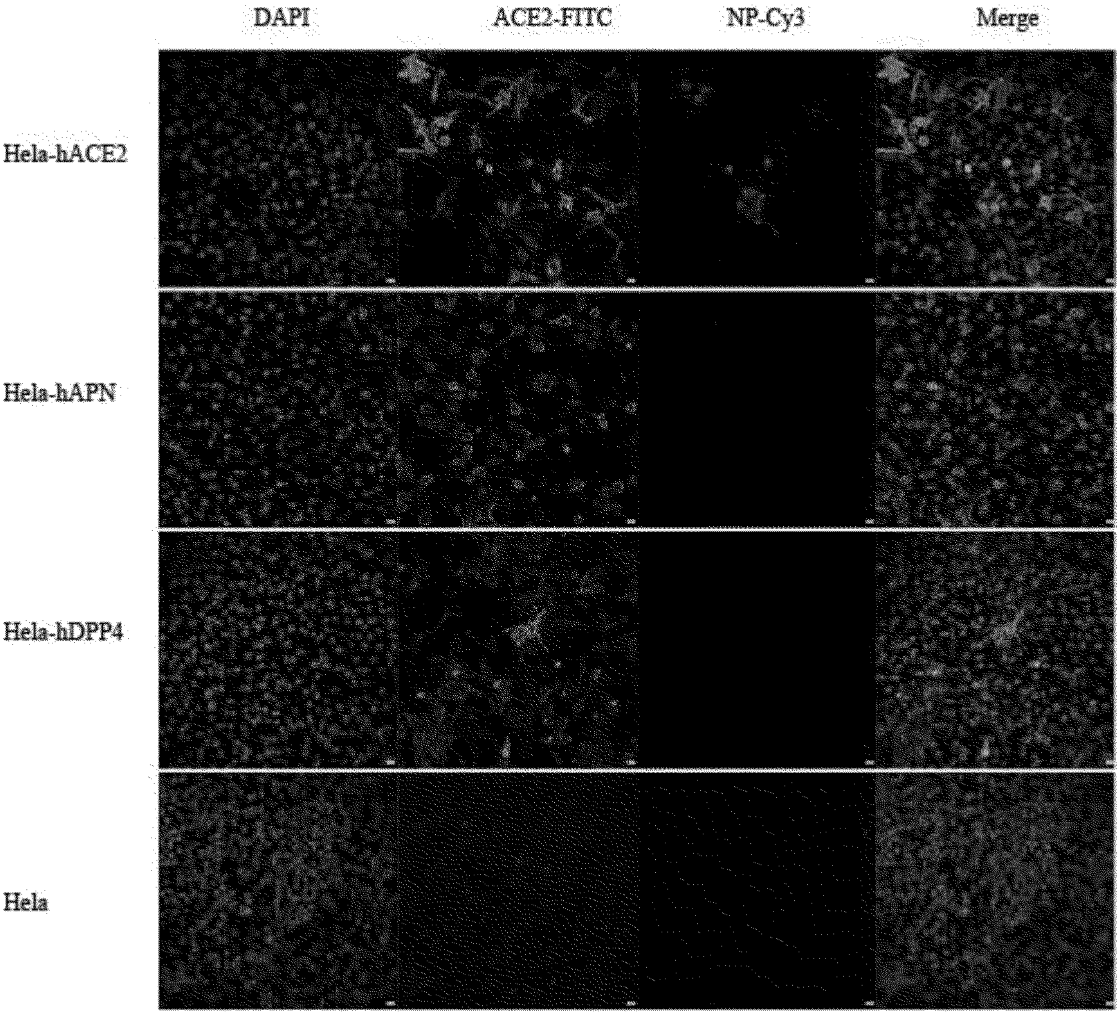
b



Extended Data Fig. 5 | Isolation and antigenic characterization of nCoV-2019. Vero E6 cells are shown at 24 hours post infection with mock (**a**) or nCoV-2019 (**b**). **c** and **d** are mock or nCoV-2019 infected samples stained with rabbit serum raised against recombinant SARSr-CoV Rp3 N protein (red) and DAPI (blue). The experiment was conducted two times independently with similar results. **e** and **f,** pie charts illustrating ratio of reads number related to nCoV-2019 among total viral related reads in metagenomics analysis of Vero (**e**) and Huh7 (**f**) cell culture supernatant.



Extended Data Fig. 6 | Analysis of nCoV-2019 receptor usage. Determination of virus infectivity in HeLa cells with or without the expression of human APN and DPP4. ACE2 protein (green), viral protein (red) and nuclei (blue) were shown. Scale bar=10 um.



Extended Data Table 1 | Patient information and their diagnosis history (some records are missing). All patients are fresh seafood market peddlers or deliverymen except ICU-01, whose contact history is unclear. All patients were in intensive care unit (ICU) during the first investigation, and now in stable condition. Blood IgM tests have been performed for the following respiratory pathogens for all patients: legionella pneumophilia, mycoplasma pneumoniae, chlamydia pneumoniae, respiratory syncytial virus, adenovirus, rickettsia, influenza A virus, influenza B virus, parainfluenza virus.

Patient No.	Gender	Age	Date of Onset	Date of Admission	Symptoms When Admitted	Current Status (2020.01.13)	Diagnosis history
ICU-01*	Male	62	2019.12.12	2019.12.27	fever	recover, discharged	negative
ICU-04	Male	32	2019.12.19	2019.12.29	fever, cough, dyspnea	fever, intermittent cough	negative
ICU-05	Male	40	2019.12.17	2019.12.27	fever (38 °C), expectoration, malaise, dyspnea	fever, malaise, intermittent cough	AdV (IgM)
ICU-06	Female	49	2019.12.23	2019.12.27	fever (37.9 °C), palpitation	fever, malaise, cough	Coronavirus (nt)
ICU-08	Female	52	2019.12.22	2019.12.29	fever (38.5 °C), expectoration, malaise, dyspnea	recover, discharged	Streptococcus pneumoniae (nt)
ICU-09	Male	40	2019.12.22	2019.12.28	fever (38.5 °C), expectoration	fever (38.5 °C), malaise, expectoration, dizziness	negative
ICU-10	Male	56	2019.12.20	2019.12.20	fever, dyspnea, chest tightness	fever, malaise, cough, dyspnea	negative

Extended Data Table 2 | Laboratory detection results. Samples from two patients (ICU-01 and ICU-08) were not available during the second investigation. They have been discharged from hospital. We did serial test for ICU-06 patient at the following date: 19.12.30, 19.12.31, 20.01.01 and 20.01.10, corresponding to seven, eight, nine and eighteen days upon disease onset (19.12.23). Table shows molecular and serological (IgM and IgG) detection results for nCoV-2019.

		First sampling-2019.12.30			Second sampling-2020.01.10			
Patient No.	Test No.	BALF	Oral Swab	Blood (Ab)	Oral Swab	Anal Swab	Blood (PCR)	Blood (Ab)
ICU-01	WIV01	-	+	NA	NA	NA	NA	NA
ICU-04	WIV02[#]	+	+	NA	-	-	-	+
ICU-05	WIV03	+	+	NA	-	-	-	+
ICU-06	WIV04[#*]	+	+	+	-	-	-	+
ICU-08	WIV05[#]	+	-	NA	NA	NA	NA	NA
ICU-09	WIV06[#]	+	+	NA	-	-	-	+
ICU-10	WIV07[#]	+	+	NA	-	-	-	+

Extended Data Table 3 | Genomic comparison of nCoV-2019 WIV04 with SARS-CoVs and bat SARSr-CoVs.

	Sequence identities with SARS-CoVs & bat SARSr-CoVs (nt/aa %)											
	Full-length genome	ORF1a	ORF1b	S	ORF3a	E	M	ORF6	ORF7a	ORF7b	ORF8	N
SARS-CoV GZ02	79.6	76.0/80.9	86.2/95.7	73.4/77.0	75.6/73.4	94.7/96.0	85.4/90.5	76.3/68.9	82.8/86.0	84.8/81.4	52.0/31.6	87.7/91.2
SARS-CoV BJ01	79.6	76.0/80.8	86.2/95.7	73.4/76.9	75.3/72.6	94.7/96.0	85.6/90.5	75.8/67.2	82.8/86.0	84.8/81.4	51.1/-	88.8/91.2
SARS-CoV Tor2	79.6	76.0/80.9	86.2/95.8	73.4/76.7	75.4/72.6	94.7/96.0	85.6/90.5	76.3/68.9	82.8/86.0	84.8/81.4	51.1/-	88.8/91.2
SARS-CoV SZ3	79.6	76.0/81.0	86.2/95.8	73.4/76.9	75.4/72.6	94.7/96.0	85.3/90.0	76.3/68.9	82.8/86.0	84.8/81.4	52.3/31.6	88.8/91.2
SARS-CoV PC4-227	79.5	76.0/80.8	86.1/95.6	73.4/76.7	75.5/72.6	94.7/96.0	85.1/90.0	75.8/68.9	82.8/86.0	84.8/81.4	52.3/-	88.5/90.7
Bat SARr-CoV RaTG13	96.2	96.0/98.0	97.3/99.3	93.1/97.7	96.3/97.8	99.6/100	95.5/99.6	98.4/100	95.6/97.5	99.2/97.7	97.0/95.0	96.9/99.0
Bat SARr-CoV WIV1	79.7	76.0/80.7	85.9/95.8	73.4/77.6	76.1/74.5	95.6/96.0	84.8/90.0	78.0/73.8	85.0/88.4	85.6/83.7	65.8/57.9	88.5/90.9
Bat SARSr-CoV WIV16	79.7	75.9/81.0	86.1/95.6	73.1/77.8	76.1/74.5	95.6/96.0	84.8/90.0	77.4/72.1	85.0/88.4	85.6/83.7	65.3/57.9	88.6/90.9
Bat SARSr-CoV SHC014	79.6	75.9/80.9	85.9/95.8	73.3/77.7	76.1/74.5	95.6/96.0	84.8/90.0	78.0/70.5	84.4/88.4	85.6/83.7	65.8/58.7	88.6/90.9
Bat SARSr-CoV Rs4231	79.7	76.0/81.0	86.2/95.8	72.9/77.5	75.8/74.1	94.3/94.7	84.4/90.0	76.9/67.2	85.0/88.4	85.6/83.7	65.3/57.9	88.8/91.4
Bat SARSr-CoV YNLF31C	79.0	75.7/80.6	85.8/95.7	71.4/75.5	75.0/71.2	94.3/96.0	84.7/89.6	76.9/70.5	83.1/87.6	86.4/83.7	50.3/31.3	88.3/90.5
Bat SARSr-CoV LYRa11	79.6	75.8/80.6	85.7/95.6	73.9/77.3	77.2/76.3	94.7/94.7	85.1/90.0	78.5/70.5	82.0/85.1	81.1/81.4	66.7/57.9	89.0/91.6
Bat SARSr-CoV ZC45	88.1	91.0/95.7	86.1/96.0	77.8/82.3	87.8/90.9	98.7/100	93.4/98.6	95.2/93.4	88.8/87.6	94.7/93.0	88.5/94.2	91.1/94.3
Bat SARSr-CoV ZXC21	88.0	90.9/95.7	86.2/95.8	77.1/81.7	88.9/92.0	98.7/100	93.4/98.6	95.2/93.4	89.1/88.4	95.5/93.0	88.5/94.2	91.2/94.3
Bat SARSr-CoV HuB2013	79.6	76.3/81.2	85.3/95.7	73.1/76.8	75.4/75.5	95.2/94.7	85.3/91.0	76.3/68.9	84.2/87.6	85.6/83.7	62.0/49.6	88.9/91.6
Bat SARSr-CoV GX2013	79.1	75.9/80.8	86.0/95.9	73.1/77.1	75.6/73.0	94.7/96.0	84.8/91.4	77.4/68.9	85.0/86.8	84.1/79.1	51.4/31.6	87.9/90.2
Bat SARSr-CoV SX2013	78.9	76.2/80.6	85.1/95.5	71.2/75.5	74.7/71.2	94.3/93.3	83.0/89.6	77.4/68.9	84.2/86.8	85.6/83.7	49.7/30.4	86.9/90.2
Bat SARSr-CoV SC2018	79.4	75.8/80.7	85.5/95.2	72.7/76.4	75.0/71.2	94.3/96.0	84.7/90.0	80.0/71.8	85.2/87.6	84.8/83.7	66.1/55.4	88.2/91.2
Bat SARSr-CoV Rs672	79.6	76.0/80.9	85.9/95.8	72.8/76.2	75.2/71.9	95.2/96.0	84.8/89.6	78.5/70.5	84.7/88.4	85.6/83.7	65.8/58.7	87.9/91.2
Bat SARSr-CoV Rp3	79.5	75.9/80.5	86.0/95.7	73.1/77.2	74.9/74.8	95.2/96.0	85.1/90.0	76.9/68.9	83.9/89.3	84.8/83.7	66.4/56.2	88.4/90.7
Bat SARSr-CoV Rf1	78.8	76.2/80.6	84.8/95.3	71.1/75.7	74.3/69.0	94.3/94.7	83.3/89.6	79.0/68.9	84.2/86.8	84.1/83.7	50.6/31.3	86.8/89.5
Bat SARSr-CoV HKU3-1	79.4	76.1/80.9	84.9/95.1	73.4/77.9	75.8/73.4	95.2/96.0	84.7/91.0	75.3/67.2	85.0/89.3	84.1/79.1	66.4/57.0	88.3/90.0

Extended Data Table 4 | Virus neutralization test (VNT) of serum samples. Each serum sample was tested in triplicate. Two healthy people from Wuhan, five patient serum samples and a horse anti-SARS-CoV anti-serum were used. 120 $TCID_{50}$ virus was used each well. Serum samples were used in a dilution from 1:10, 1:20, 1:40 to 1:80.

Samples	VNT titre for nCoV-2019
Healthy people #1 from Wuhan	neg
Healthy people #2 from Wuhan	neg
Horse anti-SARS-CoV serum	>1:80
WIV02	>1:80
WIV03	1:40
WIV04	>1:80
WIV06	>1:80
WIV07	>1:80

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Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin

Peng Zhou[1]*, Xing-Lou Yang[1]*, Xian-Guang Wang[2]*, Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1], Zheng-Li Shi[1]†

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Since the SARS outbreak 18 years ago, a large number of severe acute respiratory syndrome related coronaviruses (SARSr-CoV) have been discovered in their natural reservoir host, bats[1-4]. Previous studies indicated that some of those bat SARSr-CoVs have the potential to infect humans[5-7]. Here we report the identification and characterization of a novel coronavirus (nCoV-2019) which caused an epidemic of acute respiratory syndrome in humans, in Wuhan, China. The epidemic, started from December 12th, 2019, has caused 198 laboratory confirmed infections with three fatal cases by January 20th, 2020. Full-length genome sequences were obtained from five patients at the early stage of the outbreak. They are almost identical to each other and share 79.5% sequence identify to SARS-CoV. Furthermore, it was found that nCoV-2019 is 96% identical at the whole genome level to a bat coronavirus. The pairwise protein sequence analysis of seven conserved non-structural proteins show that this virus belongs to the species of SARSr-CoV. The nCoV-2019 virus was then isolated from the bronchoalveolar lavage fluid of a critically ill patient, which can be neutralized by sera from several patients. Importantly, we have confirmed that this novel CoV uses the same cell entry receptor, ACE2, as SARS-CoV.

Coronavirus has caused two large-scale pandemic in the last two decades, SARS and MERS (Middle East respiratory syndrome)[8,9]. It was generally believed that SARSr-CoV, mainly found in bats, might cause future disease outbreak[10,11]. Here we report on a series of unidentified pneumonia disease outbreaks in Wuhan, Hubei province, central China (Extended Data Figure 1). Started from a local fresh seafood market, the epidemic has resulted in 198 laboratory confirmed cases with three death according to authorities so far[12]. Typical clinical symptoms of these patients are fever, dry cough,

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dyspnea, headache, and pneumonia. Disease onset may result in progressive respiratory failure due to alveolar damage and even death. The disease was determined as viral induced pneumonia by clinicians according to clinical symptoms and other criteria including body temperature rising, lymphocytes and white blood cells decreasing (sometimes normal for the later), new pulmonary infiltrates on chest radiography, and no obvious improvement upon three days antibiotics treatment. It appears most of the early cases had contact history with the original seafood market, and no large scale of human-to-human transmission was observed so far.

Samples from seven patients with severe pneumonia (six are seafood market peddlers or delivers), who were enrolled in intensive unit cares at the beginning of the outbreak, were sent to WIV laboratory for pathogen diagnosis (Extended Data Table 1). As a CoV lab, we first used pan-CoV PCR primers to test these samples[13], considering the outbreak happened in winter and in a market, same environment as SARS. We found five PCR positive. A sample (WIV04) collected from bronchoalveolar lavage fluid (BALF) was analysed by metagenomics analysis using next-generation sequencing (NGS) to identify potential etiological agents. Of the 1582 total reads obtained after human genome filtering, 1378 (87.1%) matched sequences of SARSr-CoV (Fig. 1a). By *de novo* assembly and targeted PCR, we obtained a 29,891-bp CoV genome that shared 79.5% sequence identity to SARS-CoV BJ01 (GenBank accession number AY278488.2). This sequence has been submitted to GISAID (accession no. EPI_ISL_402124). Following the name by WHO, we tentatively call it novel coronavirus 2019 (nCoV-2019). Four more full-length genome sequences of nCoV-2019 (WIV02, WIV05, WIV06, and WIV07) (GISAID accession nos.

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EPI_ISL_402127-402130) that were above 99.9% identical to each other were subsequently obtained from other four patients (Extended Data Table 2).

The virus genome consists of six major open reading frames (ORFs) common to coronaviruses and a number of other accessory genes (Fig. 1b). Further analysis indicates that some of the nCoV-2019 genes shared less than 80% nt sequence identity to SARS-CoV. However, the seven conserved replicase domains in ORF1ab that were used for CoV species classification, are 94.6% aa sequence identical between nCoV-2019 and SARS-CoV, implying the two belong to same species (Extended Data Table 3).

We then found a short RdRp region from a bat coronavirus termed BatCoV RaTG13 which we previously detected in *Rhinolophus affinis* from Yunnan Province showed high sequence identity to nCoV-2019. We did full-length sequencing to this RNA sample. Simplot analysis showed that nCoV-2019 was highly similar throughout the genome to RaTG13 (Fig. 1c), with 96.2% overall genome sequence identity. The phylogenetic analysis also showed that RaTG13 is the closest relative of the nCoV-2019 and form a distinct lineage from other SARSr-CoVs (Fig. 1d). The receptor binding protein spike (S) gene was highly divergent to other CoVs (Extended Data Figure 2), with less than 75% nt sequence identity to all previously described SARSr-CoVs except a 93.1% nt identity to RaTG13 (Extended Data Table 3). The S genes of nCoV-2019 and RaTG13 S gene are longer than other SARSr-CoVs. The major differences in nCoV-2019 are the three short insertions in the N-terminal domain, and four out of five key residues changes in the receptor-binding motif, in comparison

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with SARS-CoV (Extended Data Figure 3). The close phylogenetic relationship to RaTG13 provides evidence for a bat origin of nCoV-2019.

We rapidly developed a qPCR detection based on the receptor-binding domain of spike gene, the most variable region among genome (Fig. 1c). Our data show the primers could differentiate nCoV-2019 with all other human coronaviruses including bat SARSr-CoV WIV1, which is 95% identity to SARS-CoV (Extended Data Figure 4a and 4b). From the seven patients, we found nCoV-2019 positive in six BALF and five oral swab samples during the first sampling by qPCR and conventional PCR (Extended Data Figure 4c). However, we can no longer find viral positive in oral swabs, anal swabs, and blood from these patients during the second sampling (Fig. 2a). Based on these findings, we conclude that the disease should be transmitted through airway, yet we can't rule out other possibilities if the investigation extended to include more patients.

For serological detection of nCoV-2019, we used previously developed bat SARSr-CoV Rp3 nucleocapsid protein (NP) as antigen in IgG and IgM ELISA test, which showed no cross-reactivity against other human coronaviruses except SARSr-CoV[7]. As a research lab, we were only able to get five serum samples from the seven viral infected patients. We monitored viral antibody levels in one patient (ICU-06) at seven, eight, nine, and eighteen days after disease onset (Extended Data Table 2). A clear trend of IgG and IgM titre (decreased at the last day) increase was observed (Fig. 2b). For a second investigation, we tested viral antibody for five of the seven viral positive patients around twenty days after disease onset (Extended Data Table 1 and 2). All

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patient samples, but not samples from healthy people, showed strong viral IgG positive (Fig. 2b). We also found three IgM positive, indicating acute infection.

We then successfully isolated the virus (named nCoV-2019 BetaCoV/Wuhan/WIV04/2019), in Vero and Huh7 cells using BALF sample from ICU-06 patient. Clear cytopathogenic effects were observed in cells after three days incubation (Extended Data Figure 5a and 5b). The identity of the strain WIV04 was verified in Vero E6 cells by immunofluorescence microscopy using cross-reactive viral NP antibody (Extended Data Figure 5c and 5d), and by metagenomic sequencing, from which most of the reads mapped to nCoV-2019 (Extended Data Figure 5e and 5f). Viral partials in ultrathin sections of infected cells displayed typical coronavirus morphology under electron microscopy (Fig. 3). To further confirm the neutralization activity of the viral IgG positive samples, we conducted serum-neutralization assays in Vero E6 cells using the five IgG positive patient sera. We demonstrate that all samples were able to neutralize 120 TCID50 nCoV-2019 at a dilution of 1:40-1:80. We also show that this virus could be cross-neutralized by horse anti-SARS-CoV serum at dilutions 1:80, further confirming the relationship of the two viruses (Extended Data Table 4).

Angiotensin converting enzyme II (ACE2) was known as cell receptor for SARS-CoV[14]. To determine whether nCoV-2019 also use ACE2 as a cellular entry receptor, we conducted virus infectivity studies using HeLa cells expressing or not expressing ACE2 proteins from humans, Chinese horseshoe bats, civet, pig, and mouse. We show that nCoV-2019 is able to use all but mouse ACE2 as an entry receptor in the ACE2-expressing cells, but not cells without ACE2, indicating which is likely the cell

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receptor of nCoV-2019 (Fig. 4). We also proved that nCoV-2019 does not use other coronavirus receptors, aminopeptidase N and dipeptidyl peptidase 4 (Extended Data Figure 6).

The study provides the first detailed report on nCoV-2019, the likely etiology agent responsible for ongoing acute respiratory syndrome epidemic in Wuhan, central China. Viral specific nucleotide positive and viral protein seroconversion observed in all patients tested provides evidence of an association between the disease and the presence of this virus. However, there are still many urgent questions to be answered. We need more clinical data and samples to confirm if this virus is indeed the etiology agent for this epidemic. In addition, we still don't know if this virus continue evolving and become more transmissible between human-to-human. Moreover, we don't know the transmission routine of this virus among hosts yet. We showed viral positive in oral swabs, implying nCoV-2019 may be transmitted through airway. However, this needs to be confirmed by extending detection range. Finally, based on our results, it should be expected and worth to test if ACE2 targeting or SARS-CoV targeting drugs can be used for nCoV-2019 patients. At this stage, we know very little about the virus, including basic biology, animal source or any specific treatment. The almost identical sequences of this virus in different patients imply a probably recent introduction in humans, thus future surveillance on viral mutation and transmission ability and further global research attention are urgently needed.

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AUTHOR CONTRIBUTIONS: Z.L.S., P.Z., Y.Y.W., and G.F.X. conceived the study. G.S.W., C.L.H., H.D.C., F.D., Q.J.C., F.X.Z., and LLL., collected patient samples. X.L.Y., B.Y., W.Z., B.L., J.C., X.S.Z., Y.L., H.G., R.D.J., M.Q.L., Y. Chen, X.W., X.R.S., and K.Z. performed qPCR, serology, and virus culturing. L.Z., Y.Z., H.R.S., and B.H. performed genome sequencing and annotations. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to ZLS (zlshi@wh.iov.cn).

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Supplementary Information is available in the online version of the paper.

Main Figure Legend

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Fig. 1 | Genome characterization of nCoV-2019**. a**, pie chart showing metagenomics analysis of next-generation sequencing of bronchoalveolar lavage fluid from patient ICU06. **b**, Genomic organization of nCoV-2019 WIV04. **c**, Similarity plot based on the full-length genome sequence of nCoV-2019 WIV04. Full-length genome sequences of SARS-CoV BJ01, bat SARSr-CoV WIV1, bat coronavirus RaTG13 and ZC45 were used as reference sequences. **d**, Phylogenetic tree based on nucleotide sequences of complete ORF1b of coronaviruses. Software used and settings can be found in material and method section.

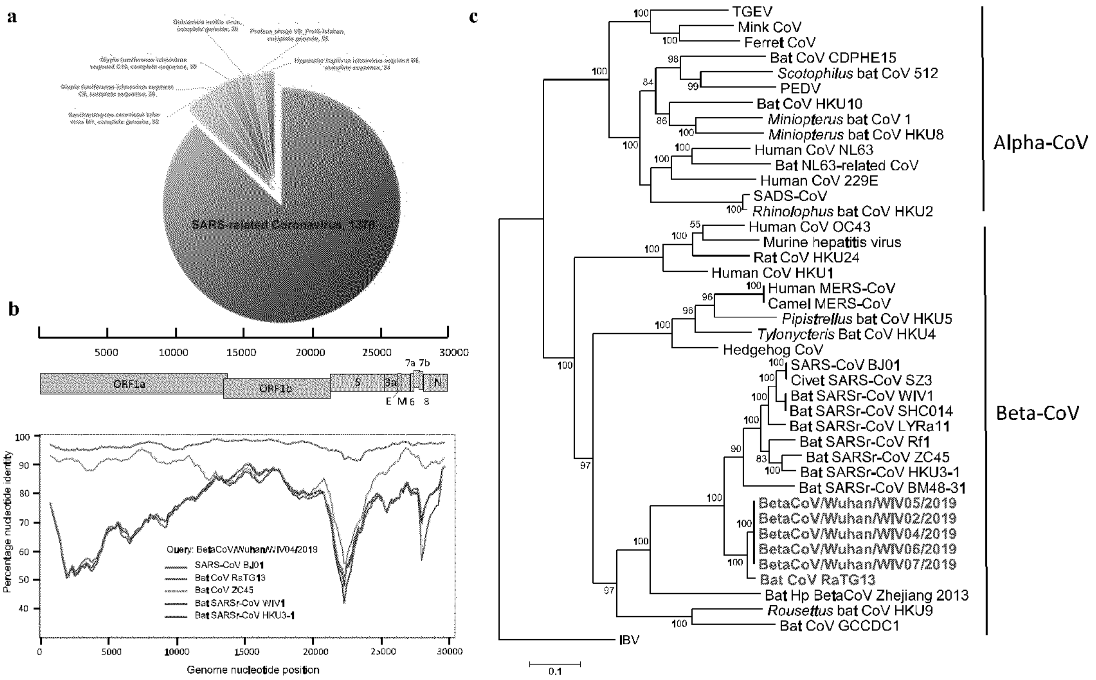

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Fig. 2 | Molecular and serological investigation of patient samples. a, molecular detection of nCoV-2019 in seven patients during two times of sampling. Patient information can be found in Extended Data Table 1 and 2. Details on detection method can be found in material and methods. BALF, bronchoalveolar lavage fluid; OS, oral swab; AS, anal swab. **b**, dynamics of nCoV-2019 antibodies in one patient who showed sign of disease on 2019.12.23 (ICU-06). **c**, serological test of nCoV-2019 antibodies in five patients (more information can be found in Extended Data Table 2). Star indicates data collected from patient ICU-06 on 2020.01.10. For b and c, cut-off was set up as 0.2 for IgM test and 0.3 for IgG test, according to healthy controls.

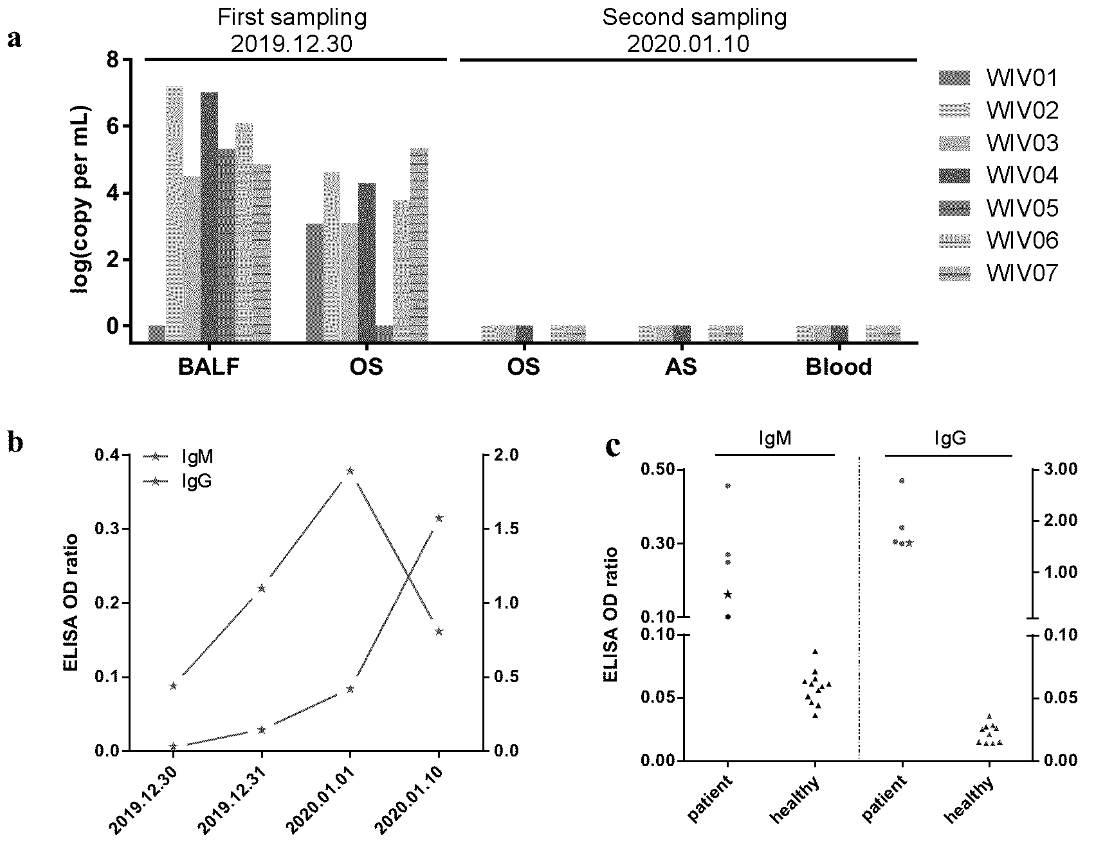

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Fig. 3 | Virions. a, viral particles in the ultrathin sections under electron microscope at 200 kV, sample from viral infected Vero E6 cells

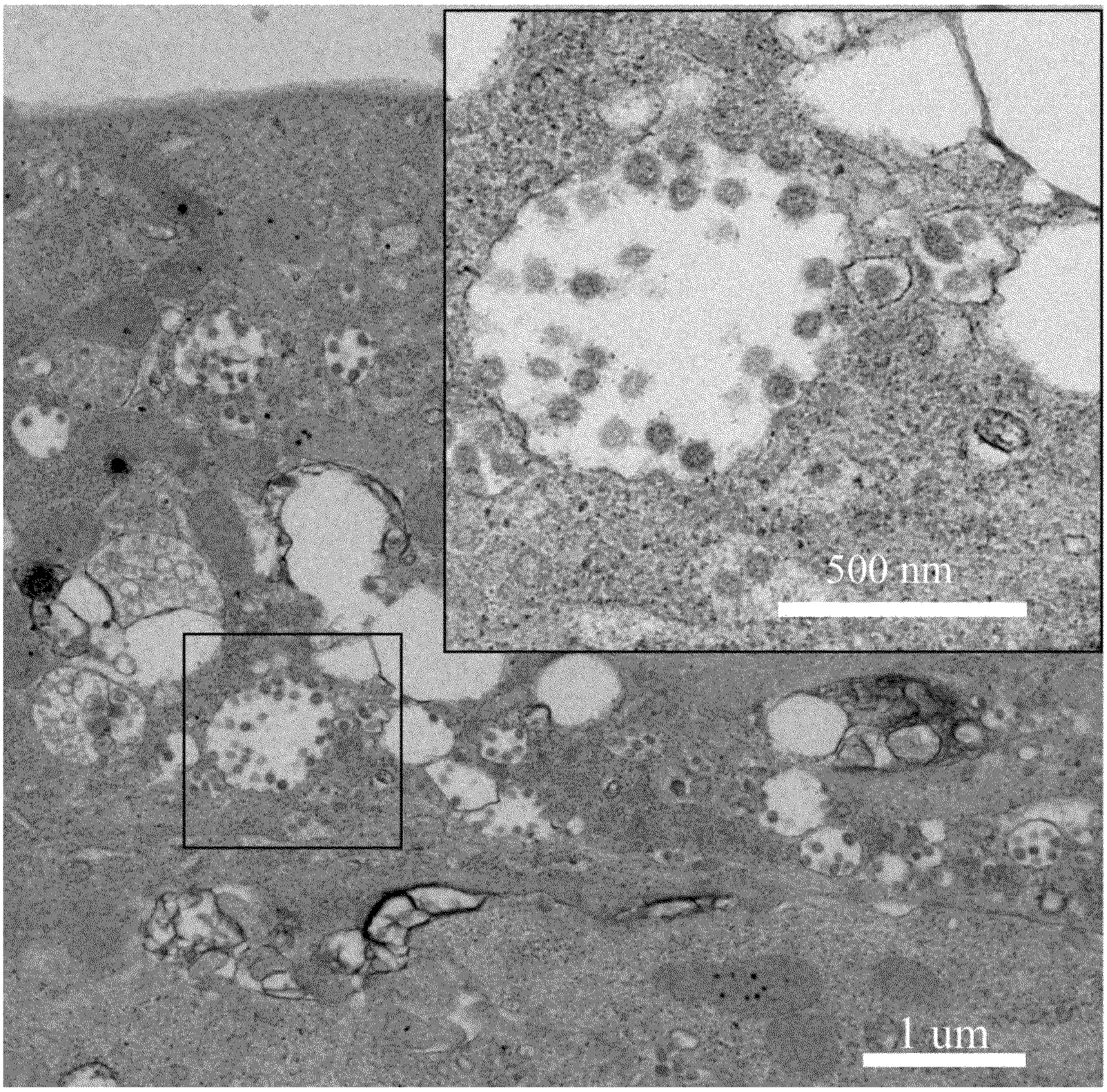

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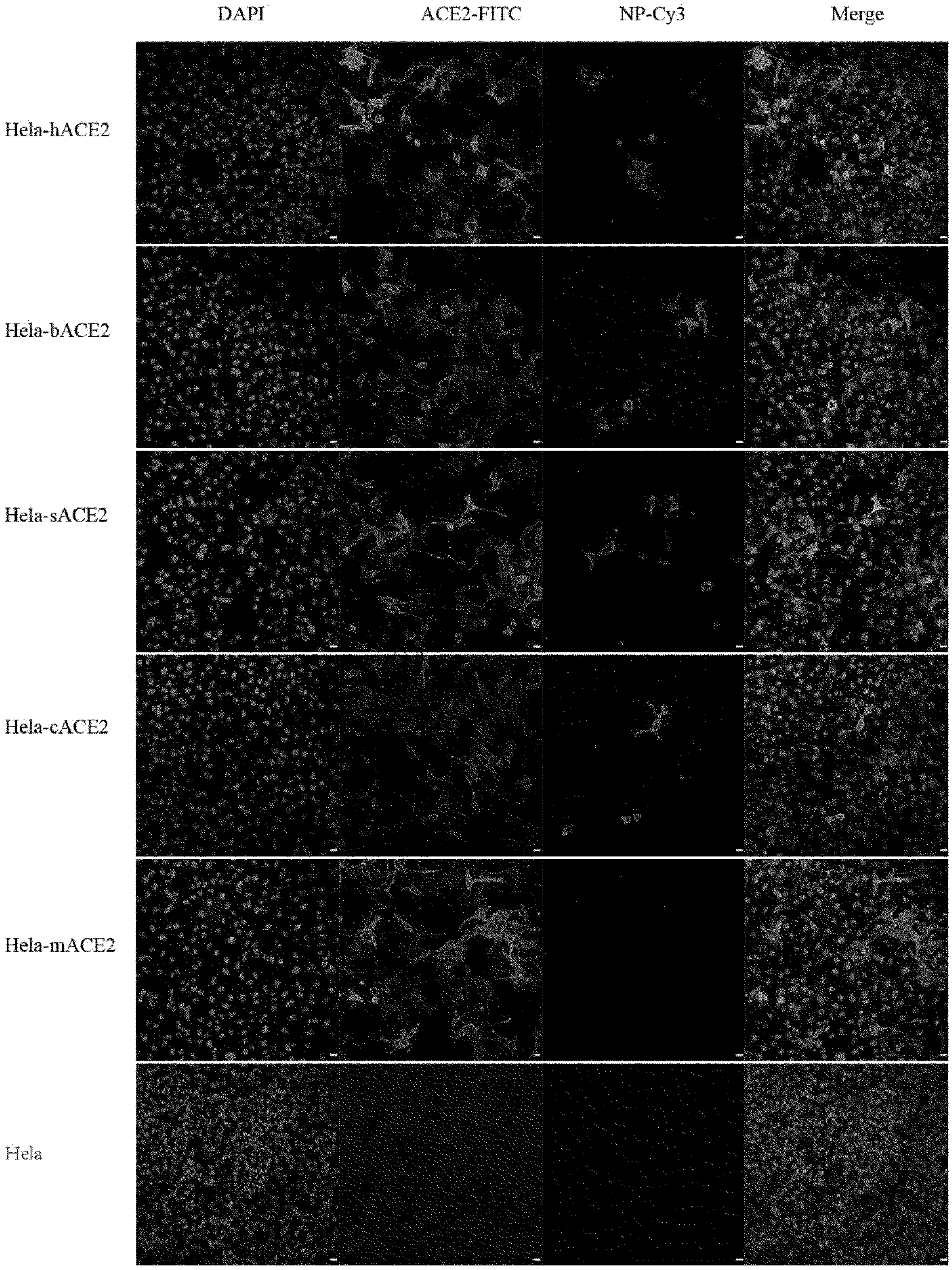
Fig. 4 | Analysis of nCoV-2019 receptor usage. Determination of virus infectivity in HeLa cells with or without the expression of ACE2. h, human; b, *Rhinolophus sinicus* bat; c, civet; s, swine (pig); m, mouse. ACE2 protein (green), viral protein (red) and nuclei (blue) was shown. Scale bar=10 um.



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METHODS

Sample collection. Human samples, including oral swabs, anal swabs, blood, and BALF samples were collected by Jinyintan hospital (Wuhan) with the consent from all patients. Patients were sampled without gender or age preference unless where indicated. For swabs, 1.5 ml DMEM+2% FBS medium was added each tube. Supernatant was collected after 2500 rpm, 60 s vortex and 15-30 min standing. Supernatant from swabs or BALF (no pretreatment) was added to either lysis buffer for RNA extraction or to viral transport medium (VTM) for virus isolation. VTM composed of Hank's balanced salt solution at pH7.4 containing BSA (1%), amphotericin (15 μg/ml), penicillin G (100 units/ml), and streptomycin (50 μg/ml). Serum was separated by centrifugation at 3,000 *g* for 15 min within 24 h of collection, followed by 56 ^{0}C 30 min inactivation, and then stored at 4 ^{0}C until use.

Virus isolation, cell infection, electron microscope and neutralization assay. The following cells were used for virus isolation in this study: Vero, Vero E6, and Huh7 that were cultured in DMEM +10% FBS. A list of cells were used for susceptibility test (Extended Data Fig. 6). All cell lines were tested free of mycoplasma contamination, applied to species identification and authenticated by microscopic morphologic evaluation. None of cell lines was on the list of commonly misidentified cell lines (by ICLAC).

Cultured cell monolayers were maintained in their respective medium. PCR-positive BALF sample from ICU-06 patient was spin at 8,000 g for 15 min, filtered and diluted 1:2 with DMEM supplied with 16 μg/ml trypsin before adding to cells. After incubation at 37 ^{0}C for 1 h, the inoculum was removed and replaced with fresh culture

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medium containing antibiotics (below) and 16 μg/ml trypsin. The cells were incubated at 37 ^{0}C and observed daily for cytopathic effect (CPE). The culture supernatant was examined for presence of virus by qRT-PCR developed in this study, and cells were examined by immunofluorescent using SARSr-CoV Rp3 NP antibody made in house (1:100). Penicillin (100 units/ml) and streptomycin (15 μg/ml) were included in all tissue culture media.

The Vero E6 cells were infected with new virus at MOI of 0.5 and harvested 48 hpi. Cells were fixed with 2.5% (wt/vol) glutaraldehyde and 1% osmium tetroxide, and then dehydrated through a graded series of ethanol concentrations (from 30 to 100%), and embedded with epoxy resin. Ultrathin sections (80 nm) of embedded cells were prepared, deposited onto Formvar-coated copper grids (200 mesh), stained with uranyl acetate and lead citrate, then observed under 200 kV Tecnai G2 electron microscope.

The virus neutralization test was carried out in a 48-well plate. The patient serum samples were heat-inactivated by incubation at 56 ^{0}C for 30 min before use. The serum samples (5 μL) were diluted to 1:10, 1:20, 1:40 or 1:80, and then an equal volume of virus stock was added and incubated at 37 ^{0}C for 60 min in a 5% CO_2 incubator. Diluted horse anti SARS-CoV serum or serum samples from healthy people were used as control. After incubation, 100 μL mixtures were inoculated onto monolayer Vero E6 cells in a 48-well plate for 1 hour. Each serum were repeated triplicate. After removing the supernatant, the plate was washed twice with DMEM medium. Cells were incubated with DMEM supplemented with 2% FBS for 24 hours. Then the cells were fixed with 4% formaldehyde. And the virus were detected using

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SL-CoV Rp3 NP antibody followed by Cy3-conjugated mouse anti-rabbit IgG. Nuclei were stained with DAPI. Infected cell number was counted by high-content cytometers.

RNA extraction and PCR. Whenever commercial kits were used, manufacturer's instructions were followed without modification. RNA was extracted from 200 μl of samples with the High Pure Viral RNA Kit (Roche). RNA was eluted in 50 μl of elution buffer and used as the template for RT-PCR.

For qPCR analysis, primers based on nCoV-2019 S gene was designed: RBD-qF1: 5'-CAATGGTTTAACAGGCACAGG-3'; RBD-qR1: 5'-CTCAAGTGTCTGTGGATCACG-3'. RNA extracted from above used in qPCR by HiScript® II One Step qRT-PCR SYBR® Green Kit (Vazyme Biotech Co.,Ltd). Conventional PCR test was also performed using the following primer pairs: ND-CoVs-951F TGTKAGRTTYCCTAAYATTAC; ND-CoVs-1805R ACATCYTGATANARAACAGC[13]. The 20 μl qPCR reaction mix contained 10 μl 2× One Step SYBR Green Mix, 1 μl One Step SYBR Green Enzyme Mix, 0.4 μl 50 × ROX Reference Dye 1, 0.4 μl of each primer (10 uM) and 2 μl template RNA. Amplification was performed as follows: 50 ^{0}C for 3 min, 95 ^{0}C for 30 s followed by 40 cycles consisting of 95 ^{0}C for 10 s, 60 ^{0}C for 30 s, and a default melting curve step in an ABI 7700 machine.

Serological test. In-house anti-SARSr-CoV IgG and IgM ELISA kits were developed using SARSr-CoV Rp3 NP as antigen, which shared above 90% amino acid identity to all SARSr-CoVs[2]. For IgG test, MaxiSorp Nunc-immuno 96 well ELISA plates

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were coated (100 ng/well) overnight with recombinant NP. Human sera were used at 1:20 dilution for 1 h at 37 ^{0}C. An anti-Human IgG-HRP conjugated monoclonal antibody (Kyab Biotech Co., Ltd, Wuhan, China) was used at a dilution of 1:40000. The OD value (450–630) was calculated. For IgM test, MaxiSorp Nunc-immuno 96 wellELISA plates were coated (500 ng/well) overnight with anti-human IgM (μ chain). Human sera were used at 1:100 dilution for 40 min at 37 ^{0}C, followed by anti-Rp3 NP-HRP conjugated (Kyab Biotech Co., Ltd, Wuhan, China) at a dilution of 1:4000. The OD value (450–630) was calculated.

Examination of ACE2 receptor for nCoV-2019 infection. HeLa cells transiently expressing ACE2 were prepared by a lipofectamine 3000 system (Thermo Fisher Scientific) in 96-well plate, with mock-transfected cells as controls. nCoV-2019 grown from Vero E6 cells was used for infection at multiplicity of infection 0.05. Same for testing of APN and DPP4. The inoculum was removed after 1 h absorption and washed twice with PBS and supplemented with medium. At 24 hpi, cells were washed with PBS and fixed with 4% formaldehyde in PBS (pH 7.4) for 20 min at room temperature. ACE2 expression was detected using mouse anti-S tag monoclonal antibody followed by FITC-labelled goat anti-mouse IgG H&L (Abcam, ab96879). Viral replication was detected using rabbit antibody against the Rp3 NP protein (made in house, 1:100) followed by cyanin 3-conjugated goat anti-rabbit IgG (1:50, Abcam, ab6939). Nucleus was stained with DAPI (Beyotime). Staining patterns were examined using the FV1200 confocal microscopy (Olympus).

High throughput sequencing, pathogen screening and genome assembly. Samples from patient BALF or from virus culture supernatant were used for RNA extraction

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and next-generation sequencing using Illumina MiSeq 3000 sequencer. Metagenomic analysis was carried out mainly base on the bioinformatics platform MGmapper (PE_2.24 and SE_2.24). The raw NGS reads were firstly processed by Cutadapt (v1.18) with minimum read length of 30bp. BWA (v0.7.12-r1039) was utilized to align reads to local database with a filter hits parameter at 0.8 FMM value and minimum alignment score at 30. Parameters for post-processing of assigned reads was set with minimum size normalized abundance at 0.01, minimum read count at 20 and other default parameters. A local nucleic acid database for human and mammals was employed to filter reads of host genomes before mapping reads to virus database. The results of metagenomic analysis were displayed through pie charts using WPS Office 2010. NGS reads were assembled into genomes using Geneious (v11.0.3) and MEGAHIT (v1.2.9). PCR and Sanger sequencing was performed to fill gaps in the genome. 5'-RACE was performed to determine the 5'-end of the genomes using SMARTer RACE 5'/3' Kit (Takara). Genomes were annotated using Clone Manager Professional Suite 8 (Sci-Ed Software).

Phylogenetic analysis. Routine sequence management and analysis was carried out using DNAStar. Sequence alignment and editing were conducted using ClustalW and GeneDoc. Maximum Likelihood phylogenetic trees based on nucleotide sequences of full-length ORF1b and S genes were constructed using the Jukes-Cantor model with bootstrap values determined by 1000 replicates in the MEGA6 software package.

Data Availability statement. Sequence data that support the findings of this study have been deposited in GISAID with the accession no. EPI_ISL_402124 and EPI_ISL_402127-402130.

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Sent: Thur 1/23/2020 6:09:05 PM (UTC-05:00)
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

I can make it.

Thanks –

Clint

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Sent: Thursday, January 23, 2020 4:40 PM
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Subject: WHO Consultation regarding the Wuhan coronavirus

Hello all,

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Please let us know if you can make it. Call in details will be sent tomorrow.

Thank you,

Bill Dowling (seconded to WHO)

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI New vaccines for a safer world

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To: William Dowling[william.dowling@cepi.net]
Cc: Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; linfa.wang@duke-nus.edu.sg[linfa.wang@duke-nus.edu.sg]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]; HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: 石正丽[zlshi@wh.iov.cn]
Sent: Thur 1/23/2020 9:06:25 PM (UTC-05:00)
Subject: Re: WHO Consultation regarding the Wuhan coronavirus

Dear William,

Thank you for the invitation. I'll be happy to participate in the discussion.

Best regards,
Zhengli,

-----原始邮件-----
发件人:"William Dowling" <william.dowling@cepi.net>
发送时间:2020-01-24 05:40:21 (星期五)
收件人: "Carolyn Clark" <carolyn.clark@cepi.net>, "Florence, Clint (NIH/NIAID) [E]" <clint.florence@nih.gov>, "larry.wolfraim@nih.gov" <larry.wolfraim@nih.gov>, "Raul Gomez Roman" <raul.gomezroman@cepi.net>, "Miles.Carroll@phe.gov.uk" <Miles.Carroll@phe.gov.uk>, "barney.graham@nih.gov" <barney.graham@nih.gov>, "Schmaljohn, Connie (NIH/NIAID) [E]" <connie.schmaljohn@nih.gov>, "Michael.holbrook@nih.gov" <Michael.holbrook@nih.gov>, "lisa.hensley@nih.gov" <lisa.hensley@nih.gov>, "rbaric@email.unc.edu" <rbaric@email.unc.edu>, "vincent.munster@nih.gov" <vincent.munster@nih.gov>, "daszak@ecohealthalliance.org" <daszak@ecohealthalliance.org>, "b.haagmans@erasmusmc.nl" <b.haagmans@erasmusmc.nl>, "Vasan, Vasan (H&B, Geelong AAHL)" <Vasan.Vasan@csiro.au>, "linfa.wang@duke-nus.edu.sg" <linfa.wang@duke-nus.edu.sg>, "jokim@ivi.int" <jokim@ivi.int>, "mksong@ivi.int" <mksong@ivi.int>, "Volker.gerdts@usask.ca" <Volker.gerdts@usask.ca>, "Giada.Mattiuzzo@nibsc.org" <Giada.Mattiuzzo@nibsc.org>, "zlshi@wh.iov.cn" <zlshi@wh.iov.cn>, "Barbara.Schnierle@pei.de" <Barbara.Schnierle@pei.de>, "leejooyeon@korea.kr" <leejooyeon@korea.kr>, "limhy0919@korea.kr" <limhy0919@korea.kr>, "Damon, Inger K. (CDC/OID/NCEZID)" <iad7@cdc.gov>, "christian.brechot@pasteur.fr" <christian.brechot@pasteur.fr>, "Kayvon Modjarrad" <kmodjarrad@eidresearch.org>
抄送: "HENAO RESTREPO, Ana Maria" <henaorestrepoa@who.int>, "GSELL, Pierre" <gsellp@who.int>, "COSTA, Alejandro Javier" <costaa@who.int>, "RIVEROS BALTA, Alina Ximena" <lauriex@who.int>
主题: WHO Consultation regarding the Wuhan coronavirus

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To: William Dowling[william.dowling@cepi.net]; Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; linfa.wang@duke-nus.edu.sg[linfa.wang@duke-nus.edu.sg]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]
Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Christian BRECHOT[christian.brechot@pasteur.fr]
Sent: Thur 1/23/2020 9:32:15 PM (UTC-05:00)
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

The Global Virus network will participate
Best regards
Christian Bréchot

De : William Dowling [mailto:william.dowling@cepi.net]
Envoyé : jeudi 23 janvier 2020 22:40
À : Carolyn Clark <carolyn.clark@cepi.net>; Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov>; larry.wolfraim@nih.gov; Raul Gomez Roman <raul.gomezroman@cepi.net>; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E] <connie.schmaljohn@nih.gov>; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL) <Vasan.Vasan@csiro.au>; linfa.wang@duke-nus.edu.sg; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/OID/NCEZID) <iad7@cdc.gov>; Christian BRECHOT <christian.brechot@pasteur.fr>; Kayvon Modjarrad <kmodjarrad@eidresearch.org>
Cc : HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
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To: William Dowling[william.dowling@cepi.net]; Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; linfa.wang@duke-nus.edu.sg[linfa.wang@duke-nus.edu.sg]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]
Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Kayvon Modjarrad[kmodjarrad@eidresearch.org]
Sent: Thur 1/23/2020 9:42:57 PM (UTC-05:00)
Subject: Re: WHO Consultation regarding the Wuhan coronavirus

Thanks Bill. I'll be available.

KM

Kayvon Mc
Director, I
Walter Re

Department of the Army
O
M

E1 kayvon.modjarrad.civ@mail.mil
E2 kmodjarrad@hivresearch.org

From: William Dowling <william.dowling@cepi.net>
Sent: Thursday, January 23, 2020 4:40 PM
To: Carolyn Clark; Florence, Clint (NIH/NIAID) [E]; larry.wolfraim@nih.gov; Raul Gomez Roman; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E]; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL); linfa.wang@duke-nus.edu.sg; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/OID/NCEZID); christian.brechot@pasteur.fr; Kayvon Modjarrad
Cc: HENAO RESTREPO, Ana Maria; GSELL, Pierre; COSTA, Alejandro Javier; RIVEROS BALTA, Alina Ximena
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To: Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]
Cc: William Dowling[william.dowling@cepi.net]; Carolyn Clark[carolyn.clark@cepi.net]; Wolfraim, Larry (NIH/NIAID) [E][larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Carroll, Miles[miles.carroll.phe.gov.uk@external.domain]; Graham, Barney (NIH/VRC) [E][bgraham@mail.nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Holbrook, Michael (NIH/NIAID) [C][michael.holbrook@nih.gov]; Hensley, Lisa (NIH/NIAID) [E][lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; linfa.wang@duke-nus.edu.sg[linfa.wang@duke-nus.edu.sg]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/DDID/NCEZID/DHCPP)[iad7@CDC.GOV]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]; HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]
Sent: Thur 1/23/2020 9:50:16 PM (UTC-05:00)
Subject: Re: WHO Consultation regarding the Wuhan coronavirus

I will make it, thank you kindly.

Professor S.S. Vasan DPhil(Oxon) FRES FRSPH

Honorary Visiting Professor - University of York

Senior Principal Research Consultant

Team Leader - Dangerous Pathogens

CSIRO Health & Biosecurity

E vasan.vasan@csiro.au

M -

T

W https://www.csiro.au/en/Locations/Vic/Geelong-AAHL

Sent from iPhone XS Max

On 24 Jan 2020, at 10:10 am, Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov> wrote:

I can make it.

Thanks –

Clint

From: William Dowling <william.dowling@cepi.net>
Sent: Thursday, January 23, 2020 4:40 PM
To: Carolyn Clark <carolyn.clark@cepi.net>; Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov>; Wolfraim, Larry (NIH/NIAID) [E] <larry.wolfraim@nih.gov>; Raul Gomez Roman <raul.gomezroman@cepi.net>; Carroll, Miles <miles.carroll.phe.gov.uk@external.domain>; Graham, Barney (NIH/VRC) [E] <bgraham@mail.nih.gov>; Schmaljohn, Connie (NIH/NIAID) [E] <connie.schmaljohn@nih.gov>; Holbrook, Michael (NIH/NIAID) [C]

<michael.holbrook@nih.gov>; Hensley, Lisa (NIH/NIAID) [E] <lisa.hensley@nih.gov>; Baric, Ralph <rbaric@email.unc.edu>; Munster, Vincent (NIH/NIAID) [E] <vincent.munster@nih.gov>; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL) <Vasan.Vasan@csiro.au>; linfa.wang@duke-nus.edu.sg; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/DDID/NCEZID/DHCPP) <iad7@CDC.GOV>; christian.brechot@pasteur.fr; Kayvon Modjarrad <kmodjarrad@eidresearch.org>
Cc: HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
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William Dowling, PhD

Non-Clinical Vaccine Development Leader

<image001.png>

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(+1) (m)

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<image002.png> <image003.png>

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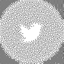

To: William Dowling[william.dowling@cepi.net]; Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]
Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Wang Linfa[linfa.wang@duke-nus.edu.sg]
Sent: Fri 1/24/2020 1:32:54 AM (UTC-05:00)
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

Thanks Bill.

Yes I will attend.

LF

Linfa (Lin-Fa) WANG, PhD FTSE
Professor & Director
Programme in Emerging Infectious Disease
Duke-NUS Medical School,
8 College Road, Singapore 169857
Tel:

From: William Dowling <william.dowling@cepi.net>
Sent: Friday, 24 January 2020 5:40 AM
To: Carolyn Clark <carolyn.clark@cepi.net>; Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov>; larry.wolfraim@nih.gov; Raul Gomez Roman <raul.gomezroman@cepi.net>; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E] <connie.schmaljohn@nih.gov>; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL) <Vasan.Vasan@csiro.au>; Wang Linfa <linfa.wang@duke-nus.edu.sg>; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/OID/NCEZID) <iad7@cdc.gov>; christian.brechot@pasteur.fr; Kayvon Modjarrad <kmodjarrad@eidresearch.org>
Cc: HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
Subject: WHO Consultation regarding the Wuhan coronavirus

- External Email -

Hello all,

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Please let us know if you can make it. Call in details will be sent tomorrow.

Thank you,

Bill Dowling (seconded to WHO)

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI New vaccines for a safer world

(+1) (o)
(+1) (m)

William.dowling@cepi.net

1901 Pensylvania Ave, NW, Suite 1003, Washington, DC 20006 USA

www.cepi.net

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Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Jae Ouk Kim[jokim@ivi.int]
Sent: Fri 1/24/2020 3:58:09 AM (UTC-05:00)
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

Dear Bill,
Thanks for your organizing a call. I will attend.
Best regards
Jae-Ouk

Jae-Ouk Kim, Ph.D.
Senior Research Scientist
Molecular Immunology, Science Unit
International Vaccine Institute (IVI)
T - (Dir) E jokim@ivi.int
W www.ivi.int

International Vaccine Institute

Please consider the environment before printing this email.

From: William Dowling [mailto:william.dowling@cepi.net]
Sent: Friday, January 24, 2020 5:48 PM
To: Wang Linfa; Carolyn Clark; Florence, Clint (NIH/NIAID) [E]; larry.wolfraim@nih.gov; Raul Gomez Roman; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E]; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL); Jae Ouk Kim; Manki Song; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/OID/NCEZID); christian.brechot@pasteur.fr; Kayvon Modjarrad
Cc: HENAO RESTREPO, Ana Maria; GSELL, Pierre; COSTA, Alejandro Javier; RIVEROS BALTA, Alina Ximena
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Dear Lin-Fa,
This is 9 PM Central Europe time on Friday Jan 24. I will be sending an outlook invite shortly with call -in details and agenda.
Thank you
Bill

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Cc: HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

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Do you mean 9 PM Central European time on Friday 24 Jan or Saturday 25 Jan as we received your email on Friday 24 Jan.

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Bill Dowling (seconded to WHO)

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI New vaccines for a safer world

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To: malik[malik@hku.hk]; Degrace, Marciela (NIH/NIAID) [E][marciela.degrace@nih.gov]; Webby, Richard[Richard.Webby@STJUDE.ORG]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; Richard Rothman[rrothma1@jhmi.edu]; Pekosz, Andrew S.[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@STJUDE.ORG]; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'Perlman, Stanley'[stanley-perlman@uiowa.edu]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; zhuhch[zhuhch@hku.hk]; Aubree Gordon[gordonal@umich.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]
Cc: Post, Diane (NIH/NIAID) [E][postd@niaid.nih.gov]; Embry, Alan (NIH/NIAID) [E][embrya@niaid.nih.gov]; Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]
From: Ghazi Kayali[ghazi@human-link.org]
Sent: Fri 1/24/2020 4:20:03 AM (UTC-05:00)
Subject: RE: Wuhan - scheduling weekly investigator calls

Either work for me.

Ghazi Kayali, PhD, MPH

Chief Executive Officer
Human Link

Adjunct Assistant Professor
University of Texas Health Sciences Center
Department of Epidemiology, Human Genetics, and Environmental Sciences
Houston, Texas

Office Tel.
Office Fax
GSM Mobile

Office Address : 3rd Floor, Camelia II Building,
Said Freiha Street,
Hazmieh,
Baabda, Lebanon

Email : ghazi@human-link.org

From: malik <malik@hku.hk>
Sent: Friday, January 24, 2020 2:10 AM
To: Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov>; Webby, Richard <Richard.Webby@STJUDE.ORG>; Ghazi Kayali <ghazi@human-link.org>; Yoshi Kawaoka <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; Richard Rothman <rrothma1@jhmi.edu>; Pekosz, Andrew S. <apekosz@jhsph.edu>; Schultz-Cherry, Stacey <Stacey.Schultz-Cherry@STJUDE.ORG>; Orenstein, Walter <worenst@emory.edu>; Lowen, Anice <anice.lowen@emory.edu>; Baric, Ralph <rbaric@email.unc.edu>; 'Perlman, Stanley' <stanley-perlman@uiowa.edu>; daszak@ecohealthalliance.org; zhuhch <zhuhch@hku.hk>; Aubree Gordon <gordonal@umich.edu>; Munster, Vincent (NIH/NIAID) [E] <vincent.munster@nih.gov>
Cc: Post, Diane (NIH/NIAID) [E] <postd@niaid.nih.gov>; Embry, Alan (NIH/NIAID) [E] <embrya@niaid.nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>
Subject: Re: Wuhan - scheduling weekly investigator calls

I am OK for either Tuesday or Wednesday.

Suggest you also invite Leo Poon and Guan Yi to join all.

E mail llmpoon@hku.hk

E mail yguan@hku.hk

Malik

From: Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov>
Sent: Thursday, January 23, 2020 23:32
To: Webby, Richard; malik; Ghazi Kayali; Yoshi Kawaoka; R.A.M. Fouchier; 'adolfo.garcia-sastre@mssm.edu'; Richard Rothman; Pekosz, Andrew S.; Schultz-Cherry, Stacey; 'david_topham@urmc.rochester.edu'; Orenstein, Walter; Lowen, Anice; Baric, Ralph; 'Perlman, Stanley'; daszak@ecohealthalliance.org; zhuhch; Aubree Gordon; Munster, Vincent (NIH/NIAID) [E]
Cc: Post, Diane (NIH/NIAID) [E]; Embry, Alan (NIH/NIAID) [E]; Lampley, Rebecca (NIH/VRC) [F]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Wuhan - scheduling weekly investigator calls

Hi everyone,

Given the escalating rate of infections with the new coronavirus, we would like to plan a **weekly meeting** with investigators working on coronaviruses. Our hopes is that we can all share information we have regarding research and sample progress on the virus, and we at NIAID can share any information and resource updates with all of you.

I know everyone's schedules are quite busy at this point. Given the time zones everyone works in we are thinking **Tuesdays at 9am** or **Wednesdays at 9am.** Please let me know by Friday if you have any strong preference, and we will get an invitation and call in sent out for next week.

Thank you!

Marciela and Erik

To: William Dowling[william.dowling@cepi.net]
Cc: Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot@pasteur.fr[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]; HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Wang Linfa[linfa.wang@duke-nus.edu.sg]
Sent: Fri 1/24/2020 5:23:36 AM (UTC-05:00)
Subject: Re: WHO Consultation regarding the Wuhan coronavirus

Thanks for clarification!

Sent from my iPhone

On 24 Jan 2020, at 4:47 PM, William Dowling <william.dowling@cepi.net> wrote:

- External Email -

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Bill

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Non-Clinical Vaccine Development Leader

<image004.png>

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(+1) (m)

William.dowling@cepi.net

1901 Pensylvania Ave, NW, Suite 1003, Washington, DC 20006 USA

www.cepi.net

<image006.png> <image008.png>

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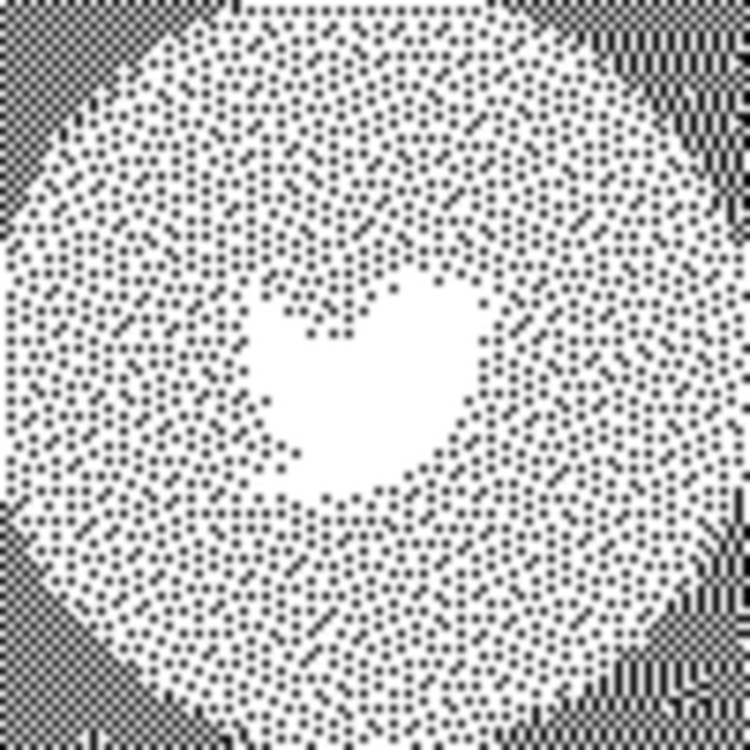

To: Marciela Degrace[marciela.degrace@nih.gov]
Cc: Richard Webby[Richard.Webby@STJUDE.ORG]; malik[malik@hku.hk]; Ghazi Kayali[ghazi@human-link.org]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; Adolfo Garcia-Sastre[Adolfo.Garcia-Sastre@mssm.edu]; Richard Rothman[rrothma1@jhmi.edu]; Andrew Pekosz[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@STJUDE.ORG]; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Perlman, Stanley[stanley-perlman@uiowa.edu]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; zhu huachen[zhuhch@hku.hk]; Aubree Gordon[gordonal@umich.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]; Diane Post[postd@niaid.nih.gov]; Embry, Alan (NIH/NIAID) [E][embrya@niaid.nih.gov]; Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]
From: Topham, David[David_Topham@URMC.Rochester.edu]
Sent: Fri 1/24/2020 9:22:05 AM (UTC-05:00)
Subject: Re: Wuhan - scheduling weekly investigator calls

Wednesday at 9AM works for me.
Dave

On Jan 23, 2020, at 10:32 AM, Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov> wrote:

Hi everyone,

Given the escalating rate of infections with the new coronavirus, we would like to plan a **weekly meeting** with investigators working on coronaviruses. Our hopes is that we can all share information we have regarding research and sample progress on the virus, and we at NIAID can share any information and resource updates with all of you.

I know everyone's schedules are quite busy at this point. Given the time zones everyone works in we are thinking **Tuesdays at 9am** or **Wednesdays at 9am.** Please let me know by Friday if you have any strong preference, and we will get an invitation and call in sent out for next week.

Thank you!

Marciela and Erik

To: Baric, Ralph S[rbaric@email.unc.edu]; Peter Daszak[daszak@ecohealthalliance.org]
From: Baric, Toni C[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=6A7390851CF045E8BE4BB68C16F4F916-TONI C BARI]
Sent: Fri 1/24/2020 9:25:55 AM (UTC-05:00)
Subject: RE: Wuhan - scheduling weekly investigator calls

Hi Peter,
Please add me to your list serve to help with Ralph's schedule. Ralph will be unavailable on 1/28 and 1/29 but more flexible in the following weeks.
Toni

From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Thursday, January 23, 2020 6:35 PM
To: Peter Daszak <daszak@ecohealthalliance.org>; Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov>; Webby, Richard <Richard.Webby@STJUDE.ORG>; malik <malik@hku.hk>; Ghazi Kayali <ghazi@human-link.org>; Yoshi Kawaoka <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; 'adolfo.garcia-sastre@mssm.edu'; Richard Rothman <rrothma1@jhmi.edu>; Pekosz, Andrew S. <apekosz@jhsph.edu>; Schultz-Cherry, Stacey <Stacey.Schultz-Cherry@STJUDE.ORG>; 'david_topham@urmc.rochester.edu'; Orenstein, Walter <worenst@emory.edu>; Lowen, Anice <anice.lowen@emory.edu>; 'Perlman, Stanley' <stanley-perlman@uiowa.edu>; zhu huachen <zhuhch@hku.hk>; Aubree Gordon <gordonal@umich.edu>; vincent.munster_nih.gov vincent.munster@nih.gov <vincent.munster@nih.gov>
Cc: Post, Diane (NIH/NIAID) [E] <postd@niaid.nih.gov>; Embry, Alan (NIH/NIAID) [E] <embrya@niaid.nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Baric, Toni C <antoinette_baric@med.unc.edu>
Subject: RE: Wuhan - scheduling weekly investigator calls

I can likely do either Tuesday or wed at 9. ralph

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Thursday, January 23, 2020 3:38 PM
To: Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov>; Webby, Richard <Richard.Webby@STJUDE.ORG>; malik <malik@hku.hk>; Ghazi Kayali <ghazi@human-link.org>; Yoshi Kawaoka <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; 'adolfo.garcia-sastre@mssm.edu'; Richard Rothman <rrothma1@jhmi.edu>; Pekosz, Andrew S. <apekosz@jhsph.edu>; Schultz-Cherry, Stacey <Stacey.Schultz-Cherry@STJUDE.ORG>; 'david_topham@urmc.rochester.edu'; Orenstein, Walter <worenst@emory.edu>; Lowen, Anice <anice.lowen@emory.edu>; Baric, Ralph S <rbaric@email.unc.edu>; 'Perlman, Stanley' <stanley-perlman@uiowa.edu>; zhu huachen <zhuhch@hku.hk>; Aubree Gordon <gordonal@umich.edu>; vincent.munster_nih.gov vincent.munster@nih.gov <vincent.munster@nih.gov>
Cc: Post, Diane (NIH/NIAID) [E] <postd@niaid.nih.gov>; Embry, Alan (NIH/NIAID) [E] <embrya@niaid.nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>
Subject: RE: Wuhan - scheduling weekly investigator calls

Thanks Marciela – I can definitely do Wednesdays at 9am, but Mondays clash with other standing meetings.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.

Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

From: Degrace, Marciela (NIH/NIAID) [E] [mailto:marciela.degrace@nih.gov]
Sent: Thursday, January 23, 2020 10:33 AM
To: Webby, Richard; malik; Ghazi Kayali; Yoshi Kawaoka; R.A.M. Fouchier; 'adolfo.garcia-sastre@mssm.edu'; Richard Rothman; Pekosz, Andrew S.; Schultz-Cherry, Stacey; 'david_topham@urmc.rochester.edu'; Orenstein, Walter; Lowen, Anice; Baric, Ralph; 'Perlman, Stanley'; Peter Daszak; zhu huachen; Aubree Gordon; vincent.munster_nih.gov vincent.munster@nih.gov
Cc: Post, Diane (NIH/NIAID) [E]; Embry, Alan (NIH/NIAID) [E]; Lampley, Rebecca (NIH/VRC) [F]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Wuhan - scheduling weekly investigator calls
Importance: High

Hi everyone,

Given the escalating rate of infections with the new coronavirus, we would like to plan a **weekly meeting** with investigators working on coronaviruses. Our hopes is that we can all share information we have regarding research and sample progress on the virus, and we at NIAID can share any information and resource updates with all of you.

I know everyone's schedules are quite busy at this point. Given the time zones everyone works in we are thinking **Tuesdays at 9am** or **Wednesdays at 9am.** Please let me know by Friday if you have any strong preference, and we will get an invitation and call in sent out for next week.

Thank you!

Marciela and Erik

To: William Dowling[william.dowling@cepi.net]; Carolyn Clark[carolyn.clark@cepi.net]; Florence, Clint (NIH/NIAID) [E][clint.florence@nih.gov]; larry.wolfraim@nih.gov[larry.wolfraim@nih.gov]; Raul Gomez Roman[raul.gomezroman@cepi.net]; Miles.Carroll@phe.gov.uk[Miles.Carroll@phe.gov.uk]; barney.graham@nih.gov[barney.graham@nih.gov]; Schmaljohn, Connie (NIH/NIAID) [E][Connie.schmaljohn@nih.gov]; Michael.holbrook@nih.gov[Michael.holbrook@nih.gov]; lisa.hensley@nih.gov[lisa.hensley@nih.gov]; Baric, Ralph S[rbaric@email.unc.edu]; vincent.munster@nih.gov[vincent.munster@nih.gov]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Vasan, Vasan (H&B, Geelong AAHL)[Vasan.Vasan@csiro.au]; jokim@ivi.int[jokim@ivi.int]; mksong@ivi.int[mksong@ivi.int]; Volker.gerdts@usask.ca[Volker.gerdts@usask.ca]; Giada.Mattiuzzo@nibsc.org[Giada.Mattiuzzo@nibsc.org]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Barbara.Schnierle@pei.de[Barbara.Schnierle@pei.de]; leejooyeon@korea.kr[leejooyeon@korea.kr]; limhy0919@korea.kr[limhy0919@korea.kr]; Damon, Inger K. (CDC/OID/NCEZID)[iad7@cdc.gov]; christian.brechot[christian.brechot@pasteur.fr]; Kayvon Modjarrad[kmodjarrad@eidresearch.org]
Cc: HENAO RESTREPO, Ana Maria[henaorestrepoa@who.int]; GSELL, Pierre[gsellp@who.int]; COSTA, Alejandro Javier[costaa@who.int]; RIVEROS BALTA, Alina Ximena[lauriex@who.int]
From: Wang Linfa[linfa.wang@duke-nus.edu.sg]
Sent: Fri 1/24/2020 2:48:49 PM (UTC-05:00)
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

Got it. Thanks and talk soon

Linfa (Lin-Fa) WANG, PhD FTSE
Professor & Director
Programme in Emerging Infectious Disease
Duke-NUS Medical School,
8 College Road, Singapore 169857
Tel:

From: William Dowling <william.dowling@cepi.net>
Sent: Saturday, 25 January 2020 3:41 AM
To: Carolyn Clark <carolyn.clark@cepi.net>; Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov>; larry.wolfraim@nih.gov; Raul Gomez Roman <raul.gomezroman@cepi.net>; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E] <Connie.schmaljohn@nih.gov>; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL) <Vasan.Vasan@csiro.au>; Wang Linfa <linfa.wang@duke-nus.edu.sg>; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; Damon, Inger K. (CDC/OID/NCEZID) <iad7@cdc.gov>; christian.brechot <christian.brechot@pasteur.fr>; Kayvon Modjarrad <kmodjarrad@eidresearch.org>
Cc: HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
Subject: RE: WHO Consultation regarding the Wuhan coronavirus

- External Email -

Hello all
I sent an outlook invite to everyone on this list. But if you did not get it, the call in information is below.
Bill

Join Skype Meeting
Trouble Joining? Try Skype Web App

Join by phone

Find a local number

Conference ID:

Forgot your dial-in PIN? | Help

From: William Dowling
Sent: Thursday, January 23, 2020 10:40 PM
To: Carolyn Clark <carolyn.clark@cepi.net>; Florence, Clint (NIH/NIAID) [E] <clint.florence@nih.gov>; larry.wolfraim@nih.gov; Raul Gomez Roman <raul.gomezroman@cepi.net>; Miles.Carroll@phe.gov.uk; barney.graham@nih.gov; Schmaljohn, Connie (NIH/NIAID) [E] <connie.schmaljohn@nih.gov>; Michael.holbrook@nih.gov; lisa.hensley@nih.gov; rbaric@email.unc.edu; vincent.munster@nih.gov; daszak@ecohealthalliance.org; b.haagmans@erasmusmc.nl; Vasan, Vasan (H&B, Geelong AAHL) <Vasan.Vasan@csiro.au>; linfa.wang@duke-nus.edu.sg; jokim@ivi.int; mksong@ivi.int; Volker.gerdts@usask.ca; Giada.Mattiuzzo@nibsc.org; zlshi@wh.iov.cn; Barbara.Schnierle@pei.de; leejooyeon@korea.kr; limhy0919@korea.kr; lad7@cdc.gov; christian.brechot@pasteur.fr; Kayvon Modjarrad <kmodjarrad@eidresearch.org>
Cc: HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; GSELL, Pierre <gsellp@who.int>; COSTA, Alejandro Javier <costaa@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>
Subject: WHO Consultation regarding the Wuhan coronavirus

Hello all,

On behalf of the WHO R&D Blueprint team, I am writing to request your participation on a call tomorrow at 9 PM Central European time (which will be Saturday morning for some of you). The purpose of the call is to lend your expertise to coordination of WHO response efforts. To that end , we would like to discuss the current status of efforts to culture the Wuhan coronavirus (or generate a recombinant virus); recent sequence data and modeling of the Spike protein; and potential next steps to assess cross reactivity with other coronaviruses. We realize that this is very short notice, but the situation is very dynamic. This would be an initial call with lengthier and more detailed calls in the near future.

Also, for those who have not seen them, I am attaching two reports on this topic that just came out and are highly relevant to the conversation.

Please let us know if you can make it. Call in details will be sent tomorrow.

Thank you,

Bill Dowling (seconded to WHO)

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI New vaccines for a safer world

(+1) (o)
(+1) (m)

William.dowling@cepi.net

1901 Pensylvania Ave, NW, Suite 1003, Washington, DC 20006 USA

www.cepi.net

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To: 'Chakravarti, Aravinda'[Aravinda.Chakravarti@nyulangone.org]; 'andersen@scripps.edu'[andersen@scripps.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'trevor@bedford.io'[trevor@bedford.io]; Peter Daszak (daszak@ecohealthalliance.org)[daszak@ecohealthalliance.org]; 'dgriffi6@jhmi.edu'[dgriffi6@jhmi.edu]; Gigi Gronvall[ggronvall@jhu.edu]; 'tinglesby@jhu.edu'[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]; 'KATHRYBR'[KATHRYBR@dni.gov]; Tony Fauci (afauci@niaid.nih.gov)[afauci@niaid.nih.gov]; Hassell, David (Chris) (OS/ASPR/IO)[David.Hassell@hhs.gov]; 'Mex7@cdc.gov'[Mex7@cdc.gov]; 'rlbull@fbi.gov'[rlbull@fbi.gov]; 'Watson, Ian D. EOP/OSTP'[Ian.D.Watson@ostp.eop.gov]; Kadlec, Robert (OS/ASPR/IO)[Robert.Kadlec@hhs.gov]; 'Conrad, Patricia (NIH/NIAID) [E]'[conradpa@niaid.nih.gov]; Barasch, Kimberly (NIH/NIAID) [C][kimberly.barasch@nih.gov]
Cc: May, David[DMay@nas.edu]; Chao, Samantha[SChao@nas.edu]; Laney, Kara N.[KLaney@nas.edu]; Shore, Carolyn[CShore@nas.edu]; Shelton Davenport, Marilee[MShelton@nas.edu]; Symmes, Gregory[GSymmes@nas.edu]; Brown, Lisa[LBrown@nas.edu]; Downey, Autumn[ADowney@nas.edu]; Wollek, Scott[SWollek@nas.edu]; Kanarek, Morgan[MKanarek@nas.edu]; Dzau, Victor J.[VDzau@nas.edu]; Beachy, Sarah[SBeachy@nas.edu]; Logan, Kendall[KLogan@nas.edu]; Kearney, Megan[MKearney@nas.edu]; Korsen, Dana[DKorsen@nas.edu]; Behney, Clyde[CBehney@nas.edu]; Shern, Lauren[LShern@nas.edu]; Borel, Bridget[BBorel@nas.edu]
From: Pope, Andrew[APope@nas.edu]
Sent: Mon 2/3/2020 12:04:47 PM (UTC-05:00)
Subject: Today's Call/meeting info
Agenda- 2019-nCoV.docx
SOW.docx

Thank you for participating in today's meeting of experts at the National Academies to discuss and identify what data, information and samples are needed to understand the evolutionary origins of 2019-nCoV and more effectively respond to the outbreak and resulting misinformation.

Attached for your information are:
Agenda
Scope of Work
A list of participants will be sent along shortly

Please let me know if you have any questions of problems with connecting.

"Zoom" Call-in info is as follows (and is included at top of agenda):

Zoom Dial-in Info:
Time: Feb 3, 2020 02:00 PM Eastern Time (US and Canada)
Join from PC, Mac, Linux, iOS or Android: https://nasem.zoom.us/
Telephone:
Meeting ID:
International numbers available: https://nasem.zoom.us/

Andrew M. Pope, Ph.D.
Director
Board on Health Sciences Policy
Health and Medicine Division
The National Academies of Sciences,
Engineering, and Medicine
apope@nas.edu
direct
office
Find us at nationalacademies.org/HMD

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Expert Meeting

Rapid Response for Assessment of Data Needs for 2019-nCoV

Agenda

February 3, 2020
2:00 p.m.–3:00 p.m. (ET)

Keck Center, Room 103
500 5th St NW, Washington, DC 20001

Join from PC, Mac, Linux, iOS or Android: https://nasem.zoom.us/
Telephone:
Meeting ID:
International numbers available: https://nasem.zoom.us/

Meeting Objective: *Assess what data, information and samples are needed to understand the evolutionary origins of 2019-nCoV and more effectively respond to the outbreak and resulting misinformation.*

2:00 p.m. **Welcome and Introductions** (*5 mins*)

ANDREW POPE
Director, Board on Health Sciences Policy
National Academies of Sciences, Engineering, and Medicine

2:05 p.m. **Statement of Work** (*10 mins*)

KELVIN DROEGEMEIER
Director
Office of Science and Technology Policy

D. CHRISTIAN ("CHRIS") HASSELL
Senior Science Advisor
U.S. Department of Health and Human Services

2:15 p.m. **Perspective from NIH/NIAID** (*10 mins*)

ANTHONY ("TONY") S. FAUCI
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

2:25 p.m.	**Discussion of Meeting Objective** (*30 mins*)
2:55 p.m.	**Determine Next Steps** (*5 mins*)
3:00 p.m.	**Adjourn**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Statement of Work

Rapid Response for Assessment of Data Needs for 2019-nCoV

February 3, 2020

Statement of Task:

In response to a request from OSTP, the NASEM will examine information and identify data requirements that would help determine the origins of 2019-nCoV, specifically from an evolutionary/structural biology standpoint. NASEM will also consider whether this should include more temporally and geographically diverse clinical isolates, sequences, etc. Although a widely-disputed paper posted on a pre-print server last week has since been withdrawn, the response to that paper highlights the need to determine these information needs as quickly as possible. As part of a broader deliberative process, this review will help prepare for future events by establishing a process for quickly assembling subject matter experts for evaluation of other potentially threatening organisms.

Workplan:

NASEM will hold a meeting of experts to assess what data, information and samples are needed to address the unknowns, in order to understand the evolutionary origins of NCoV and more effectively respond to both the outbreak and any resulting misinformation. A statement from the National Academies will be prepared and published on the Web as a “Based on Science” article that summarizes the status and needs for more and what types of data. A more in-depth examination of the issues will be established as a follow up as needed.

To: 'Chakravarti, Aravinda'[Aravinda.Chakravarti@nyulangone.org]; Kristian Andersen [redacted]; Baric, Ralph S[rbaric@email.unc.edu]; Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Peter Daszak (daszak@ecohealthalliance.org)[daszak@ecohealthalliance.org]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]
Cc: Shore, Carolyn[CShore@nas.edu]; Chao, Samantha[SChao@nas.edu]
From: Pope, Andrew[APope@nas.edu]
Sent: Tue 2/4/2020 9:10:35 AM (UTC-05:00)
Subject: URGENT: Please review by NOON if at all possible...
Response Letter_DRAFT - Feb 4.docx

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a “Based on Science” web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the data needs that are identified. We think it would be helpful to be a bit more specific, but don’t want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.
Director
Board on Health Sciences Policy
Health and Medicine Division
The National Academies of Sciences,
Engineering, and Medicine
apope@nas.edu
[redacted] direct
[redacted] office
Find us at nationalacademies.org/HMD

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CONFIDENTIAL DRAFT

February 4, 2020

[insert address]

Dear XXX:

Thank you for your letter regarding the current outbreak of a new respiratory virus, the 2019 Novel Coronavirus, or 2019-nCoV, which was first detected in Wuhan, China, and has now been reported in a growing number of locations worldwide, including the United States.[1] The request from OSTP is timely given the public health urgency of the outbreak and potential for misinformation.

In response to your request, we consulted leading experts[2] in the fields of virology, infectious disease genomics, genome sciences, epidemiology, microbiology, immunobiology, coronaviruses, emerging infections, biosecurity, and global health, to share their views of whether available genomic data on 2019-nCoV are consistent with natural evolution and the data that could help determine the origins of 2019-nCoV, specifically from an evolutionary and structural biology standpoint.

Many studies of the genome of 2019-nCoV to better understand its origin and how it relates to viruses found in bats and other species are already underway.[3] The initial views of the experts[4] is that the available genomic data are consistent with natural evolution[5] and that there is currently no evidence that the virus was engineered to spread more quickly among humans. [ask experts to add specifics re binding sites?] They also told us that additional genomic sequence data from geographically and temporally diverse viral samples, including samples that have been collected prior to the outbreak in Wuhan, could be used to clarify the origins of the virus. Understanding the driving forces behind viral evolution may facilitate the development of more effective strategies for managing the 2019-nCoV outbreak. International collaboration is more important than ever to overcome these types of global challenges.

The National Academies stand ready to assemble a committee of experts to examine these issues in more detail and provide more complete evidence-based advice to you in an expedited manner if requested.

Thank you, again for your commitment to the National Academies and our efforts to provide independent, objective analysis; advise the nation; and inform public policy decisions.

Sincerely,

---

[1] "2019 Novel Coronavirus (2019-nCoV) Situation Summary." *Centers for Disease Control and Prevention*, 3 Feb. 2020. https://www.cdc.gov/coronavirus/2019-nCoV/summary.html#anchor_1580079137454. Accessed 3 Feb. 2020.

[2] [possible add list]

[3] [insert references]

[5] [possibly add brief explanation that this does not preclude an unintentional release from a laboratory studying the evolution of related coronaviruses]

cc: [insert names]

To: Leo Poon[llmpoon@hku.hk]; Webby, Richard[Richard.Webby@STJUDE.ORG]; malik[malik@hku.hk]; Ghazi Kayali[ghazi@human-link.org]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; yguan@hku.hk[yguan@hku.hk]; 'adolfo.garcia-sastre@mssm.edu'['adolfo.garcia-sastre@mssm.edu']; Richard Rothman[rrothma1@jhmi.edu]; Pekosz, Andrew S.[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@STJUDE.ORG]; 'david_topham@urmc.rochester.edu'['david_topham@urmc.rochester.edu']; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'Perlman, Stanley'[stanley-perlman@uiowa.edu]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; zhu huachen[zhuhch@hku.hk]; Aubree Gordon[gordonal@umich.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]; PETERPALESE[peter.palese@mssm.edu]; 'Krammer, Florian' (florian.krammer@mssm.edu)[florian.krammer@mssm.edu]; Ben Cowling[bcowling@hku.hk]; larry.anderson@emory.edu[larry.anderson@emory.edu]; jwramme@emory.edu[jwramme@emory.edu]; aneesh.mehta@emory.edu[aneesh.mehta@emory.edu]; Baric, Toni C[antoinette_baric@med.unc.edu]; MASATO HATTA[masato.hatta@wisc.edu]; Gabriele Neumann (gabriele.neumann@wisc.edu)[gabriele.neumann@wisc.edu]; Subbarao, Kanta[kanta.subbarao@influenzacentre.org]
Cc: Fry, Alicia (CDC/DDID/NCIRD/ID)[agf1@CDC.GOV]; Pallansch, Mark A. (CDC/DDID/NCIRD/DVD)[map1@CDC.GOV]; Hall, Aron (CDC/DDID/NCIRD/DVD)[esg3@CDC.GOV]; Post, Diane (NIH/NIAID) [E][postd@niaid.nih.gov]; Embry, Alan (NIH/NIAID) [E][embrya@niaid.nih.gov]; Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]; Andy Pekosz[apekosz1@jhu.edu]; Topham, David[David_Topham@URMC.Rochester.edu]; Gerber, Susan I. (CDC/DDID/NCIRD/DVD)[bhx1@cdc.gov]; zhuhuachen@gmail.com[zhuhuachen@gmail.com]
From: Degrace, Marciela (NIH/NIAID) [E][marciela.degrace@nih.gov]
Sent: Tue 2/4/2020 9:23:34 AM (UTC-05:00)
Subject: RE: nCoV weekly investigators meeting

Apologies to everyone who got a reminder email this morning for the incorrect link. If you had trouble joining, the proper meeting link is below:

https://global.gotomeeting.com/join/

You can also dial in using your phone.
United States:

Access Code:

To: Pope, Andrew[APope@nas.edu]
Cc: Chakravarti, Aravinda[Aravinda.Chakravarti@nyulangone.org]; Kristian Andersen ; Baric, Ralph S[rbaric@email.unc.edu]; Trevor Bedford[trevor@bedford.io]; Peter Daszak (daszak@ecohealthalliance.org)[daszak@ecohealthalliance.org]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Shore, Carolyn[CShore@nas.edu]; Chao, Samantha[SChao@nas.edu]
From: Perlman, Stanley[stanley-perlman@uiowa.edu]
Sent: Tue 2/4/2020 11:21:18 AM (UTC-05:00)
Subject: Re: URGENT: Please review by NOON if at all possible...

I would add to one of the sentences that Trevor suggested modifying to state: They also told us that additional genomic sequence data from geographically and temporally diverse viral samples, including samples that have been collected prior to the outbreak in Wuhan, could be used to clarify the origins of the virus and **to assess whether virus is evolving to better infect or be transmissible between humans, as occurred during the SARS epidemic**.
On another note, as I thought about our discussion last night, I could think of no examples of CoV evolving on passage in cultured cells to encode a furin site at the S1-S2 cleavage site. The cleavage sites are so variable among CoV that there is no need to invoke evolution in cultured cells (as I think we concluded yesterday).

Stanley Perlman, MD, Ph.D.
Professor
Depts of Microbiology and Immunology, and Pediatrics
BSB 3-712
University of Iowa
Iowa City, IA 52242

On Feb 4, 2020, at 9:14 AM, Trevor Bedford <trevor@bedford.io> wrote:

Briefly, my suggestions:

1. I wouldn't mention binding sites here. If you start weighing evidence there's a lot to consider for both scenarios.

2. I would say "no evidence of genetic engineering" full stop.

3. Rather than "including samples that have been collected prior to the outbreak in Wuhan" I would say "including samples collected from as early as possible in the Wuhan outbreak".

I'm not sure what the exact capacity of this group going forward will be, but I might suggest moving to more secure forms of communication.

- Trevor

On Feb 4, 2020, at 6:10 AM, Pope, Andrew <APope@nas.edu> wrote:

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a “Based on Science” web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the

data needs that are identified. We think it would be helpful to be a bit more specific, but don't want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.
Director
Board on Health Sciences Policy
Health and Medicine Division
The National Academies of Sciences,
Engineering, and Medicine
apope@nas.edu
direct
office
Find us at nationalacademies.org/HMD

<image001.png>

<Response Letter_DRAFT - Feb 4.docx>

To: Peter Daszak[daszak@ecohealthalliance.org]
Cc: Pope, Andrew[APope@nas.edu]; Chakravarti, Aravinda[Aravinda.Chakravarti@nyulangone.org]; Baric, Ralph S[rbaric@email.unc.edu]; Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]; Shore, Carolyn[CShore@nas.edu]; Chao, Samantha[SChao@nas.edu]
From: Kristian G. Andersen
Sent: Tue 2/4/2020 12:05:54 PM (UTC-05:00)
Subject: Re: URGENT: Please review by NOON if at all possible...

I too agree with all that has been said, but would caution against adding language suggesting that the virus might evolve (i.e., "mutate" to most people) towards better infectivity or transmission - a lot has been said about that for Ebola and other viruses, and it's been driving fear because most people don't fully understand what it means. I'm not arguing that it's not something that might well happen - the SARS data beautifully show it - but I would be worried about the message it could send.

Reading through the letter I think it's great, but I do wonder if we need to be more firm on the question of engineering. The main crackpot theories going around at the moment relate to this virus being somehow engineered with intent and that is demonstrably not the case. Engineering can mean many things and could be done for either basic research or nefarious reasons, but the data conclusively show that neither was done (in the nefarious scenario somebody would have used a SARS/MERS backbone and optimal ACE2 binding as previously described, and for the basic research scenario would have used one of the many already available reverse genetic systems). If one of the main purposes of this document is to counter those fringe theories, I think it's very important that we do so strongly and in plain language ("consistent with" [natural evolution] is a favorite of mine when talking to scientists, but not when talking to the public - especially conspiracy theorists).

Best,
Kristian

On Tue, Feb 4, 2020 at 9:02 AM Peter Daszak <daszak@ecohealthalliance.org> wrote:

I agree with all of the other comments so far sent in, and want to add the following:

1) In the 3rd paragraph, it's important to add "including further samples from wildlife", and perhaps the rationale for this "to identify other viruses closely related to nCoV"

2) Re. references for #3 that there are current and planned studies underway on the bat origins of CoVs. Here are some references to pick from if they make sense:

- Latinne A, Hu B, Olival KJ, et al.; Origin and cross-species transmission of bat coronaviruses in China. *Nature Communications* 2020;**In review**.
- Wang N, Li S-Y, Yang X-L, et al.; Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China. *Virologica Sinica* 2018. doi: 10.1007/s12250-018-0012-7.
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- Zhou P, Fan H, Lan T, et al.; Fatal Swine Acute Diarrhea Syndrome caused by an HKU2-related Coronavirus of Bat Origin. *Nature* 2018

Cheers,

Peter

Peter Daszak

President

EcoHealth Alliance

460 West 34th Street – 17th Floor

New York, NY 10001

Tel.

Website: www.ecohealthalliance.org

Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

From: Pope, Andrew [mailto:APope@nas.edu]
Sent: Tuesday, February 4, 2020 9:11 AM
To: 'Chakravarti, Aravinda'; Kristian Andersen ; Ralph Baric (rbaric@email.unc.edu); Trevor Bedford (trevor@bedford.io); Peter Daszak; Gigi Gronvall; Tom Inglesby (tinglesby@jhu.edu); Stanley Perlman (stanley-perlman@uiowa.edu)
Cc: Shore, Carolyn; Chao, Samantha
Subject: URGENT: Please review by NOON if at all possible...
Importance: High

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Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the data needs that are identified. We think it would be helpful to be a bit more specific, but don't want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.

Director

Board on Health Sciences Policy

Health and Medicine Division

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apope@nas.edu

direct

office

Find us at nationalacademies.org/HMD

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To: Peter Daszak[daszak@ecohealthalliance.org]; Pope, Andrew[APope@nas.edu]; 'Chakravarti, Aravinda'[Aravinda.Chakravarti@nyulangone.org]; Kristian Andersen [redacted]; Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]
Cc: Shore, Carolyn[CShore@nas.edu]; Chao, Samantha[SChao@nas.edu]
From: Baric, Ralph S[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB0D9CC80C184735A4E862C3BDD8A15D-RALPH S BAR]
Sent: Tue 2/4/2020 12:24:05 PM (UTC-05:00)
Subject: RE: URGENT: Please review by NOON if at all possible...
Response Letter_DRAFT - Feb 4-rsb.docx

I also agree with the other comments. However, I do think we need to say that the closest relative to this virus (96%) was identified from bats circulating in a cave in Yunnan, China. This makes a strong statement for animal origin. I have included a more articulate sentence in the draft document.

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, February 4, 2020 12:01 PM
To: Pope, Andrew <APope@nas.edu>; 'Chakravarti, Aravinda' <Aravinda.Chakravarti@nyulangone.org>; Kristian Andersen [redacted]; Baric, Ralph S <rbaric@email.unc.edu>; Trevor Bedford (trevor@bedford.io) <trevor@bedford.io>; Gigi Gronvall <ggronvall@jhu.edu>; Tom Inglesby (tinglesby@jhu.edu) <tinglesby@jhu.edu>; Stanley Perlman (stanley-perlman@uiowa.edu) <stanley-perlman@uiowa.edu>
Cc: Shore, Carolyn <CShore@nas.edu>; Chao, Samantha <SChao@nas.edu>
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Importance: High

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1) In the 3rd paragraph, it's important to add "including further samples from wildlife", and perhaps the rationale for this "to identify other viruses closely related to nCoV"
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Cheers,

Peter

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Andy

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CONFIDENTIAL DRAFT

February 4, 2020

[insert address]

Dear XXX:

Thank you for your letter regarding the current outbreak of a new respiratory virus, the 2019 Novel Coronavirus, or 2019-nCoV, which was first detected in Wuhan, China, and has now been reported in a growing number of locations worldwide, including the United States.[1] The request from OSTP is timely given the public health urgency of the outbreak and potential for misinformation.

In response to your request, we consulted leading experts[2] in the fields of virology, infectious disease genomics, genome sciences, epidemiology, microbiology, immunobiology, coronaviruses, emerging infections, biosecurity, and global health, to share their views of whether available genomic data on 2019-nCoV are consistent with natural evolution and the data that could help determine the origins of 2019-nCoV, specifically from an evolutionary and structural biology standpoint.

Many studies of the genome of 2019-nCoV to better understand its origin and how it relates to viruses found in bats and other species are already underway.[3] The initial views of the experts[4] is that the available genomic data are consistent with natural evolution[5] and that there is currently no evidence that the virus was engineered to spread more quickly among humans. [ask experts to add specifics re binding sites?] They also told us that additional genomic sequence data from geographically and temporally diverse viral samples, including samples that have been collected prior to the outbreak in Wuhan, could be used to clarify the origins of the virus. Understanding the driving forces behind viral evolution may facilitate the development of more effective strategies for managing the 2019-nCoV outbreak. International collaboration is more important than ever to overcome these types of global challenges.

The National Academies stand ready to assemble a committee of experts to examine these issues in more detail and provide more complete evidence-based advice to you in an expedited manner if requested.

Thank you, again for your commitment to the National Academies and our efforts to provide independent, objective analysis; advise the nation; and inform public policy decisions.

Sincerely,

---

[1] "2019 Novel Coronavirus (2019-nCoV) Situation Summary." *Centers for Disease Control and Prevention*, 3 Feb. 2020. https://www.cdc.gov/coronavirus/2019-nCoV/summary.html#anchor_1580079137454. Accessed 3 Feb. 2020.

[2] [possible add list]

[3] [insert references]

[5] [possibly add brief explanation that this does not preclude an unintentional release from a laboratory studying the evolution of related coronaviruses]

cc: [insert names]

To: Peter Daszak[daszak@ecohealthalliance.org]; 'Chakravarti, Aravinda'[Aravinda.Chakravarti@nyulangone.org]; Kristian Andersen ; Baric, Ralph S[rbaric@email.unc.edu]; Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]
Cc: Chao, Samantha[SChao@nas.edu]; Pope, Andrew[APope@nas.edu]
From: Shore, Carolyn[CShore@nas.edu]
Sent: Tue 2/4/2020 12:42:48 PM (UTC-05:00)
Subject: RE: URGENT: Please review by NOON if at all possible...
Lancet_genomic-characterization-2019-nCoV_2020.pdf

Thank you, all, for your input on the draft letter. A couple of clarifying questions regarding citations:

- Ralph – is the attached article the appropriate citation for your comment regarding the closest relative of 2019-nCoV or is there another citation we should reference?
- Are there any other articles that we should cite that examine the origin of 2019-nCoV specifically?

Best,
Carolyn

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, February 4, 2020 12:01 PM
To: Pope, Andrew <APope@nas.edu>; 'Chakravarti, Aravinda' <Aravinda.Chakravarti@nyulangone.org>; Kristian Andersen (KGA1978@gmail.com) <KGA1978@gmail.com>; Ralph Baric (rbaric@email.unc.edu) <rbaric@email.unc.edu>; Trevor Bedford (trevor@bedford.io) <trevor@bedford.io>; Gigi Gronvall <ggronvall@jhu.edu>; Tom Inglesby (tinglesby@jhu.edu) <tinglesby@jhu.edu>; Stanley Perlman (stanley-perlman@uiowa.edu) <stanley-perlman@uiowa.edu>
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Cheers,

Peter

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Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding

Roujian Lu, Xiang Zhao*, Juan Li*, Peihua Niu*, Bo Yang*, Honglong Wu*, Wenling Wang, Hao Song, Baoying Huang, Na Zhu, Yuhai Bi, Xuejun Ma, Faxian Zhan, Liang Wang, Tao Hu, Hong Zhou, Zhenhong Hu, Weimin Zhou, Li Zhao, Jing Chen, Yao Meng, Ji Wang, Yang Lin, Jianying Yuan, Zhihao Xie, Jinmin Ma, William J Liu, Dayan Wang, Wenbo Xu, Edward C Holmes, George F Gao, Guizhen Wu¶, Weijun Chen¶, Weifeng Shi¶, Wenjie Tan¶*

Summary

Background In late December, 2019, patients presenting with viral pneumonia due to an unidentifiedmicrobial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 novel coronavirus (2019-nCoV). As of Jan 26, 2020, more than 2000 cases of 2019-nCoV infection have been confirmed,most of which involved people living in or visiting Wuhan, and human-to-human transmission has been confirmed.

Methods We did next-generation sequencing of samples from bronchoalveolar lavage fluidand cultured isolates from nine inpatients, eight of whom had visited the Huanan seafood market in Wuhan. Complete and partial 2019-nCoV genome sequences were obtained from these individuals. Viral contigs were connected using Sanger sequencing to obtain the full-length genomes, with the terminal regions determined by rapid amplification of cDNA ends. Phylogenetic analysis of these 2019-nCoV genomes and those of other coronaviruses was used to determine the evolutionary history of the virus and help infer its likely origin. Homology modelling was done to explore the likely receptor-binding properties of the virus.

Findings The ten genome sequences of 2019-nCoV obtained from the nine patients were extremely similar, exhibiting more than 99·98% sequence identity. Notably, 2019-nCoV was closely related (with 88% identity) to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, collected in 2018 in Zhoushan, eastern China, but were more distant from SARS-CoV (about 79%) and MERS-CoV (about 50%). Phylogenetic analysis revealed that 2019-nCoV fell within the subgenus Sarbecovirus of the genus Betacoronavirus, with a relatively long branch length to its closest relatives bat-SL-CoVZC45 and bat-SL-CoVZXC21, and was genetically distinct from SARS-CoV. Notably, homology modelling revealed that 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV, despite amino acid variation at some key residues.

Interpretation 2019-nCoV is sufficientlydivergent from SARS-CoV to be considered a new human-infecting betacoronavirus. Although our phylogenetic analysis suggests that bats might be the original host of this virus, an animal sold at the seafood market in Wuhan might represent an intermediate host facilitating the emergence of the virus in humans. Importantly, structural analysis suggests that 2019-nCoV might be able to bind to the angiotensin-converting enzyme 2 receptor in humans. The future evolution, adaptation, and spread of this virus warrant urgent investigation.

Funding National Key Research and Development Program of China, National Major Project for Control and Prevention of Infectious Disease in China, Chinese Academy of Sciences, Shandong First Medical University.

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Introduction

Viruses of the family Coronaviridae possess a single-strand, positive-sense RNA genome ranging from 26 to 32 kilobases in length.[1] Coronaviruses have been identifiedin several avian hosts,[2,3] as well as in various mammals, including camels, bats, masked palm civets, mice, dogs, and cats. Novel mammalian coronaviruses are now regularly identified.[1] For example, an HKU2-related coronavirus of bat origin was responsible for a fatal acute diarrhoea syndrome in pigs in 2018.[4]

Among the several coronaviruses that are pathogenic to humans, most are associated with mild clinical symptoms,[1] with two notable exceptions: severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), a novel betacoronavirus that emerged in Guangdong, southern China, in November, 2002,[5] and resulted in more than 8000 human infections and 774 deaths in 37 countries during 2002–03;[6] and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), which was firstdetected in Saudi Arabia in 2012[7] and was responsible

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Research in context

Evidence before this study

The causal agent of an outbreak of severe pneumonia in Wuhan, China, is a novel coronavirus, provisionally named 2019 novel coronavirus (2019-nCoV). The first cases were reported in December, 2019.

Added value of this study

We have described the genomic characteristics of 2019-nCoV and similarities and differences to other coronaviruses, including the virus that caused the severe acute respiratory syndrome epidemic of 2002–03. Genome sequences of 2019-nCoV sampled from nine patients who were among the early cases of this severe infection are almost genetically identical, which suggests very recent emergence of this virus in humans and that the outbreak was detected relatively rapidly. 2019-nCoV is most closely related to other betacoronaviruses of bat origin, indicating that these animals are the likely reservoir hosts for this emerging viral pathogen.

Implications of all the available evidence

By documenting the presence of 2019-nCoV in a sample of patients, our study extends previous evidence that this virus has led to the novel pneumonia that has caused severe disease in Wuhan and other geographical localities. Currently available data suggest that 2019-nCoV infected the human population from a bat reservoir, although it remains unclear if a currently unknown animal species acted as an intermediate host between bats and humans.

for 2494 laboratory-confirmed cases of infection and 858 fatalities since September, 2012, including 38 deaths following a single introduction into South Korea.[8,9]

In late December, 2019, several patients with viral pneumonia were found to be epidemiologically associated with the Huanan seafood market in Wuhan, in the Hubei province of China, where a number of non-aquatic animals such as birds and rabbits were also on sale before the outbreak. A novel, human-infecting coronavirus,[10,11] provisionally named 2019 novel coronavirus (2019-nCoV), was identified with use of next-generation sequencing. As of Jan 28, 2020, China has reported more than 5900 confirmed and more than 90 00 suspected cases of 2019-nCoV infection across 33 Chinese provinces or municipalities, with 106 fatalities. In addition, 2019-nCoV has now been reported in Thailand, Japan, South Korea, Malaysia, Singapore, and the USA. Infections in medical workers and family clusters were also reported and human-to-human transmission has been confirmed.[12] Most of the infected patients had a high fever and some had dyspnoea, with chest radiographs revealing invasive lesions in both lungs.[12,13]

We report the epidemiological data of nine inpatients, from at least three hospitals in Wuhan, who were diagnosed with viral pneumonia of unidentified cause. Using next-generation sequencing of bronchoalveolar lavage fluid samples and cultured isolates from these patients, 2019-nCoV was found. We describe the genomic characterisation of ten genomes of this novel virus, providing important information on the origins and cell receptor binding of the virus.

Methods

Patients and samples

Nine patients with viral pneumonia and negative for common respiratory pathogens, who presented to at least three hospitals in Wuhan, were included in this study. Eight of the patients had visited the Huanan seafood market before the onset of illness, and one patient (WH04) did not visit the market but stayed in a hotel near the market between Dec 23 and Dec 27, 2019 (table). Five of the patients (WH19001, WH19002, WH19004, WH19008, and YS8011) had samples collected by the Chinese Center for Disease Control and Prevention (CDC) which were tested for 18 viruses and four bacteria using the RespiFinderSmart22 Kit (PathoFinder, Maastricht, Netherlands) on the LightCycler 480 Real-Time PCR system (Roche, Rotkreuz, Switzerland). Presence of SARS-CoV and MERS-CoV was tested using a previously reported method.[14] All five CDC samples were negative for all common respiratory pathogens screened for. Four of the patients (WH01, WH02, WH03, and WH04) had samples collected by BGI (Beijing, China), and were tested for five viruses and one bacterium using the RespiPathogen 6 Kit (Jiangsu Macro & Micro Test, Nantong, China) on the Applied Biosystems ABI 7500 Real-Time PCR system (ThermoFisher Scientific, Foster City, CA, USA). All four samples were negative for the targeted respiratory pathogens.

Virus isolation

Special-pathogen-free human airway epithelial (HAE) cells were used for virus isolation. Briefly, bronchoalveolar lavage fluids or throat swabs from the patients were inoculated into the HAE cells through the apical surfaces. HAE cells were maintained in an air–liquid interface incubated at 37°C. The cells were monitored daily for cytopathic effects by light microscopy and the cell supernatants were collected for use in quantitative RT-PCR assays. After three passages, apical samples were collected for sequencing.

BGI sequencing strategy

All collected samples were sent to BGI for sequencing. 140 μL bronchoalveolar lavage fluid samples (WH01 to WH04) were reserved for RNA extraction using the QIAamp Viral RNA Mini Kit (52904; Qiagen, Heiden, Germany), according to the manufacturer's recommendations. A probe-captured technique was used to remove human nucleic acid. The remaining RNA was

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	Patient information			Sample information			Genome sequence obtained
	Exposure to Huanan seafood market	Date of symptom onset	Admission date	Sample type	Collection date	Ct value	
Samples WH19001 and WH19005	Yes	Dec 23, 2019	Dec 29, 2019	BALF and cultured virus	Dec 30, 2019	30·23	Complete
Sample WH19002	Yes	Dec 22, 2019	NA	BALF	Dec 30, 2019	30·50	Partial (27 130 nucleotides)
Sample WH19004	Yes	NA	NA	BALF	Jan 1, 2020	32·14	Complete
Sample WH19008	Yes	NA	Dec 29, 2019	BALF	Dec 30, 2019	26·35	Complete
Sample YS8011	Yes	NA	NA	Throat swab	Jan 7, 2020	22·85	Complete
Sample WH01	Yes	NA	NA	BALF	Dec 26, 2019	32·60	Complete
Sample WH02	Yes	NA	NA	BALF	Dec 31, 2019	34·23	Partial (19 503 nucleotides)
Sample WH03	Yes	Dec 26, 2019	NA	BALF	Jan 1, 2020	25·38	Complete
Sample WH04	No*	Dec 27, 2019	NA	BALF	Jan 5, 2020	25·23	Complete

Ct=threshold cycle. BALF=bronchoalveolar lavage fluid. NA=not available. 2019-nCoV=2019 novel coronavirus. *Patient stayed in a hotel near Huanan seafood market from Dec 23 to Dec 27, 2019, and reported fever on Dec 27, 2019.

Table: **Information about samples taken from nine patients infected with 2019-nCoV**

reverse-transcribed into cDNA, followed by the second-strand synthesis. Using the synthetic double-stranded DNA, a DNA library was constructed through DNA-fragmentation, end-repair, adaptor-ligation, and PCR amplification. The constructed library was qualifiedwith an Invitrogen Qubit 2.0 Fluorometer (ThermoFisher, Foster City, CA, USA), and the qualifieddouble-stranded DNA library was transformed into a single-stranded circular DNA library through DNA-denaturation and circularisation. DNA nanoballs were generated from single-stranded circular DNA by rolling circle amplification, then qualifiedwith Qub it 2.0 and loaded onto the flowcell and sequenced with PE100 on the DNBSEQ-T7 platform (MGI, Shenzhen, China).

After removing adapter, low-quality, and low-complexity reads, high-quality genome sequencing data were generated. Sequence reads were firstfilteredagainst the human reference genome (hg19) using Burrows-Wheeler Alignment.[15] The remaining data were then aligned to the local nucleotide database (using Burrows-Wheeler Alignment) and non-redundant protein database (using RapSearch),[16] downloaded from the US National Center for Biotechnology Information website, which contain only coronaviruses that have been published. Finally, the mapped reads were assembled with SPAdes[17] to obtain a high-quality coronavirus genome sequence.

Primers were designed with use of OLIGO Primer Analysis Software version 6.44 on the basis of the assembled partial genome, and were verifiedby Prim er-Blast (for more details on primer sequencs used please contact the corresponding author). PCR was set up as follows: 4·5 μL of 10X buffer, 4 μL of dNTP mix (2·5 μmol/L), 1 μL of each primer (10 μmol/L), and 0·75 units of HS Ex Taq (Takara Biomedical Technology, Beijing, China), in a total volume of 30 μL. The cDNAs reverse transcribed from clinical samples were used as templates, and random primers were used. The following program was run on the thermocycler: 95°C for 5 min; 40 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 1 min as determined by product size; 72°C for 7 min; and a 4°C hold. Finally, the PCR products were separated by agarose gel electrophoresis, and products of the expected size were sequenced from both ends on the Applied Biosystems 3730 DNA Analyzer platform (Applied Biosystems, Life Technologies, Foster City, CA, USA; for more details on expected size please contact the corresponding author).

Chinese CDC sequencing strategy

The whole-genome sequences of 2019-nCoV from six samples (WH19001, WH19005, WH19002, WH19004, WH19008, and YS8011) were generated by a combination Sanger, Illumina, and Oxford nanopore sequencing. First, viral RNAs were extracted directly from clinical samples with the QIAamp Viral RNA Mini Kit, and then used to synthesise cDNA with the SuperScript III Reverse Transcriptase (ThermoFisher, Waltham, MA, USA) and N6 random primers, followed by second-strand synthesis with DNA Polymerase I, Large (Klenow) Fragment (ThermoFisher). Viral cDNA libraries were prepared with use of the Nextera XT Library Prep Kit (Illumina, San Diego, CA, USA), then purified with Agencourt AMPure XP beads (Beckman Coulter, Brea, CA, USA), followed by quantificationwith an Invitrogen Qub it 2.0 Fluorometer. The resulting DNA libraries were sequenced on either the MiSeq or iSeq platforms (Illumina) using a 300-cycle reagent kit. About 1·2–5 GB of data were obtained for each sample.

For the **National Center for Biotechnology Information website** see https://www.ncbi.nlm.nih.gov/

The raw fastQ filesfor each virus sample were filtered using previously described criteria,[18] then subjected to de novo assembly with the CLCBio software version 11.0.1. Mapped assemblies were also done using the bat-derived SARS-like coronavirus isolate bat-SL-CoVZC45 (accession number MG772933.1) as a reference. Variant calling, genome alignments, and sequence illustrations were generated with CLCBio software, and the

assembled genome sequences were confirmedby Sanger sequencing.

Rapid amplification of cDNA ends (RACE) was done to obtain the sequences of the 5′ and 3′ termini, using the Invitrogen 5′ RACE System and 3′ RACE System (Invitrogen, Carlsbad, CA, USA), according to the manufacturer's instructions. Gene-specific primers (appendix p 1) for 5′ and 3′ RACE PCR amplificationwe re designed to obtain a fragment of approximately 400–500 bp for the two regions. PurifiedPCR products were cloned into the pMD18-T Simple Vector (TaKaRa, Takara Biotechnology, Dalian, China) and chemically competent *Escherichia coli* (DH5α cells; TaKaRa), according to the manufacturer's instructions. PCR products were sequenced with use of M13 forward and reverse primers.

See Online for appendix

Virus genome analysis and annotation

Reference virus genomes were obtained from GenBank using Blastn with 2019-nCoV as a query. The open reading frames of the verifiedgenome sequences were predicted using Geneious (version 11.1.5) and annotated using the Conserved Domain Database.[19] Pairwise sequence identities were also calculated using Geneious. Potential genetic recombination was investigated using SimPlot software (version 3.5.1)[20] and phylogenetic analysis.

For **Genbank** see https://www.ncbi.nlm.nih.gov/genbank

For the **China National Microbiological Data Center website** see http://nmdc.cn/

For the **data from BGI on the China National GeneBank** see https://db.cngb.org/datamart/disease/DATAdis19/

Phylogenetic analysis

Sequence alignment of 2019-nCoV with reference sequences was done with Mafft software (version 7.450).[21] Phylogenetic analyses of the complete genome and major coding regions were done with RAxML software (version 8.2.9)[22] with 1000 bootstrap replicates, employing the general time reversible nucleotide substitution model.

Development of molecular diagnostics for 2019-nCoV

On the basis of the genome sequences obtained, a real-time PCR detection assay was developed. PCR primers and probes were designed using Applied Biosystems Primer Express Software (ThermoFisher Scientific,Foster City, CA, USA) on the basis of our sequenced virus genomes. The specific primers and probe set (labelled with the reporter 6-carboxyfluorescein [FA M] and the quencher Black Hole Quencher 1 [BHQ1]) for *orf1a* were as follows: forward primer 5′-AGAAGATTGGTTAGATGATGATAGT-3′; reverse primer 5′-TTCCATCTCTAATTGAGGTTGAACC-3′; and probe 5′-FAM-TCCTCACTGCCGTCTTGTTGACCA-BHQ1-3′. The human *GAPDH* gene was used as an internal control (forward primer 5′-TCAAGAAGGTGGTGAAGCAGG-3′; reverse primer 5′-CAGCGTCAAAGGTGGAGGAGT-3′; probe 5′-VIC-CCTCAAGGGCATCCTGGGCTACACT-BHQ1-3′). Primers and probes were synthesised by BGI (Beijing, China). RT-PCR was done with an Applied Biosystems 7300 Real-Time PCR System (ThermoScientific),with 3 0 µL reaction volumes consisting of 14 µL of diluted RNA, 15 µL of 2X Taqman One-Step RT-PCR Master Mix Reagents (4309169; Applied Biosystems, ThermoFisher), 0·5 µL of 40X MultiScribe and RNase inhibitor mixture, 0·75 µL forward primer (10 µmol/L), 0·75 µL reverse primer (10 µmol/L), and 0·375 µL probe (10 µmol/L). Thermal cycling parameters were 30 min at 42°C, followed by 10 min at 95°C, and a subsequent 40 cycles of amplification(95°C for 15 s and 58°C for 45 s). Fluorescence was recorded during the 58°C phase.

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of report. GFG and WS had access to all the data in the study, and GFG, WS, WT, WC, and GW were responsible for the decision to submit for publication.

Results

From the nine patients' samples analysed, eight complete and two partial genome sequences of 2019-nCoV were obtained. These data have been deposited in the China National Microbiological Data Center (accession number NMDC10013002 and genome accession numbers NMDC60013002-01 to NMDC60013002-10) and the data from BGI have been deposited in the China National GeneBank (accession numbers CNA0007332–35).

Based on these genomes, we developed a real-time PCR assay and tested the original clinical samples from the BGI (WH01, WH02, WH03, and WH04) again to determine their threshold cycle (Ct) values (table). The remaining samples were tested by a differentreal-time PCR assay developed by the Chinese CDC, with Ct values ranging from 22·85 to 32·41 (table). These results confirmed the presence of 2019-nCoV in the patients.

Bronchoalveolar lavage fluid samples or cultured viruses of nine patients were used for next-generation sequencing. After removing host (human) reads, de novo assembly was done and the contigs obtained used as queries to search the non-redundant protein database. Some contigs identified in all the samples were closely related to the bat SARS-like betacoronavirus bat-SL-CoVZC45 betacoronavirus.[23] Bat-SL-CoVZC45 was then used as the reference genome and reads from each pool were mapped to it, generating consensus sequences corresponding to all the pools. These consensus sequences were then used as new reference genomes. Eight complete genomes and two partial genomes (from samples WH19002 and WH02; table) were obtained. The de novo assembly of the clean reads from all the pools did not identify any other long contigs that corresponded to other viruses at high abundance.

The eight complete genomes were nearly identical across the whole genome, with sequence identity above 99·98%, indicative of a very recent emergence into the human population (figure 1A). The largest nucleotide difference was four mutations. Notably, the sequence identity between the two virus genomes from the same patient (WH19001, from bronchoalveolar lavage fluid, and WH19005, from cell culture) was more than 99·99%,

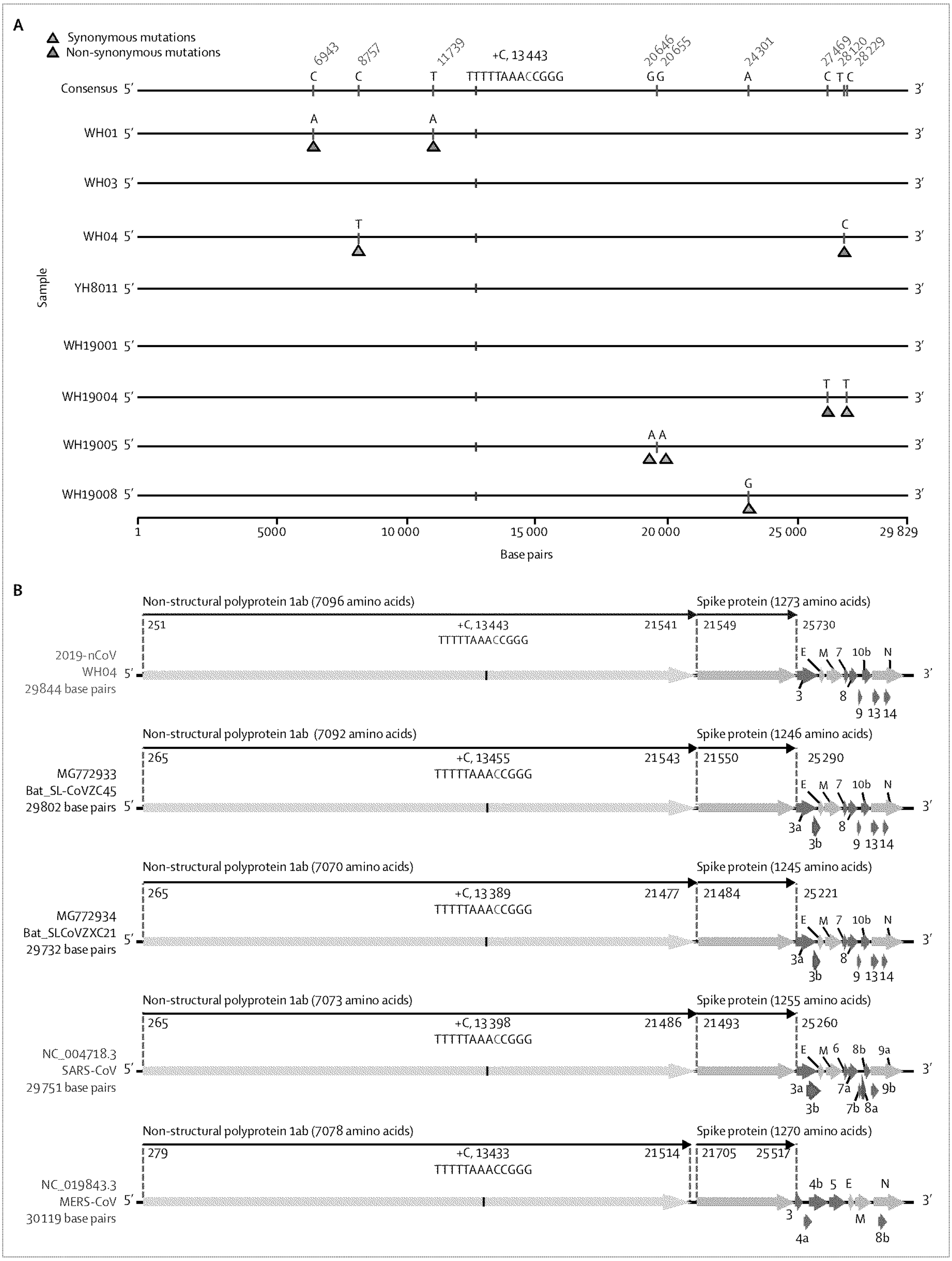

***Figure 1:* Sequence comparison and genomic organisation of 2019-nCoV**

(A) Sequence alignment of eight full-length genomes of 2019-nCoV, 29 829 base pairs in length, with a few nucleotides truncated at both ends of the genome. (B) Coding regions of 2019-nCoV, bat-SL-CoVZC45, bat-SL-CoVZXC21, SARS-CoV, and MERS-CoV. Only open reading frames of more than 100 nucleotides are shown. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus.

A

	Strain	Complete genome (%)	Gene region (%)												
			1ab	1a	1b	S	3	E	M	7	8	10b	N	13	14
Nucleotide sequences	Bat-SL-CoVZC45	87·6	88·9	90·7	86·0	75·2	87·8	98·7	93·4	95·2	88·8	88·5	91·1	89·1	96·7
	Bat-SL-CoVZXC21	87·5	88·7	90·3	86·1	74·7	88·9	98·7	93·4	95·2	89·1	88·5	91·2	89·5	96·7
	SARS-CoVGZ02	79·0	79·5	75·4	86·3	72·7	75·6	93·5	85·1	74·5	82·1	..	88·1	..	..
Amino acid sequences	Bat-SL-CoVZC45	..	95·6	95·6	95·8	80·2	90·9	100·0	98·6	93·4	87·6	94·2	94·3	73·2	92·9
	Bat-SL-CoVZXC21	..	95·2	95·1	95·5	79·6	92·0	100·0	98·6	93·4	88·4	94·2	94·3	73·2	92·9
	SARS-CoVGZ02	..	86·2	80·5	95·6	76·2	73·1	94·7	90·1	68·9	85·2	..	90·3	..	..

B

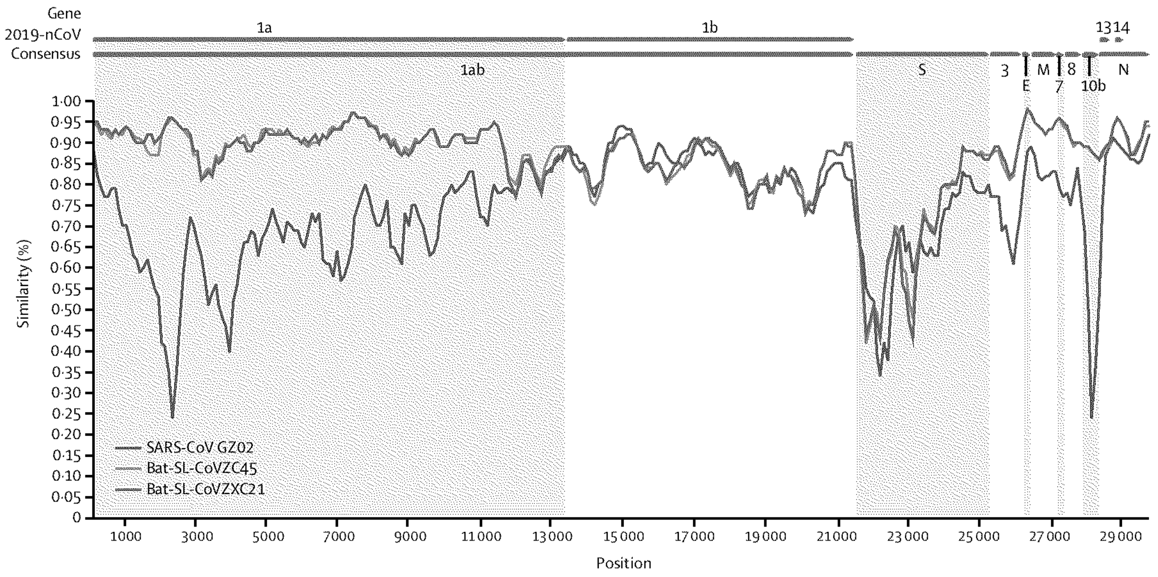

Figure 2: **Sequence identity between the consensus of 2019-nCoV and representative betacoronavirus genomes**
(A) Sequence identities for 2019-nCoV compared with SARS-CoV GZ02 (accession number AY390556) and the bat SARS-like coronaviruses bat-SL-CoVZC45 (MG772933) and bat-SL-CoVZXC21 (MG772934). (B) Similarity between 2019-nCoV and related viruses. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus.

with 100% identity at the amino acid level. In addition, the partial genomes from samples WH02 and WH19002 also had nearly 100% identity to the complete genomes across the aligned gene regions.

A Blastn search of the complete genomes of 2019-nCoV revealed that the most closely related viruses available on GenBank were bat-SL-CoVZC45 (sequence identity 87·99%; query coverage 99%) and another SARS-like betacoronavirus of bat origin, bat-SL-CoVZXC21 (accession number MG772934;[23] 87·23%; query coverage 98%). In fivege ne regions (E, M, 7, N, and 14), the sequence identities were greater than 90%, with the highest being 98·7% in the E gene (figure 2A). The S gene of 2019-nCoV exhibited the lowest sequence identity with bat-SL-CoVZC45 and bat-SL-CoVZXC21, at only around 75%. In addition, the sequence identity in 1b (about 86%) was lower than that in 1a (about 90%; figure 2A). Most of the encoded proteins exhibited high sequence identity between 2019-nCoV and the related bat-derived coronaviruses (figure 2a). The notable exception was the spike protein, with only around 80% sequence identity, and protein 13, with 73·2% sequence identity. Notably, the 2019-nCoV strains were less genetically similar to SARS-CoV (about 79%) and MERS-CoV (about 50%). The similarity between 2019-nCoV and related viruses was visualised using SimPlot software, with the 2019-nCoV consensus sequence employed as the query (figure 2B).

Comparison of the predicted coding regions of 2019-nCoV showed that they possessed a similar genomic organisation to bat-SL-CoVZC45, bat-SL-CoVZXC21, and SARS-CoV (figure 1B). At least 12 coding regions were predicted, including 1ab, S, 3, E, M, 7, 8, 9, 10b, N, 13, and 14 (figure 1B). The lengths of most of the proteins encoded by 2019-nCoV, bat-SL-CoVZC45, and bat-SL-CoVZXC21 were similar, with only a few minor insertions or deletions. A notable differencewas a longer spike protein encoded by 2019-nCoV compared with the bat SARS-like coronaviruses, SARS-CoV, and MERS-CoV (figure 1B).

Phylogenetic analysis of 2019-nCoV and its closely related reference genomes, as well as representative betacoronaviruses, revealed that the fivesubg enera formed fivew ell supported branches (figure 3). The subgenus

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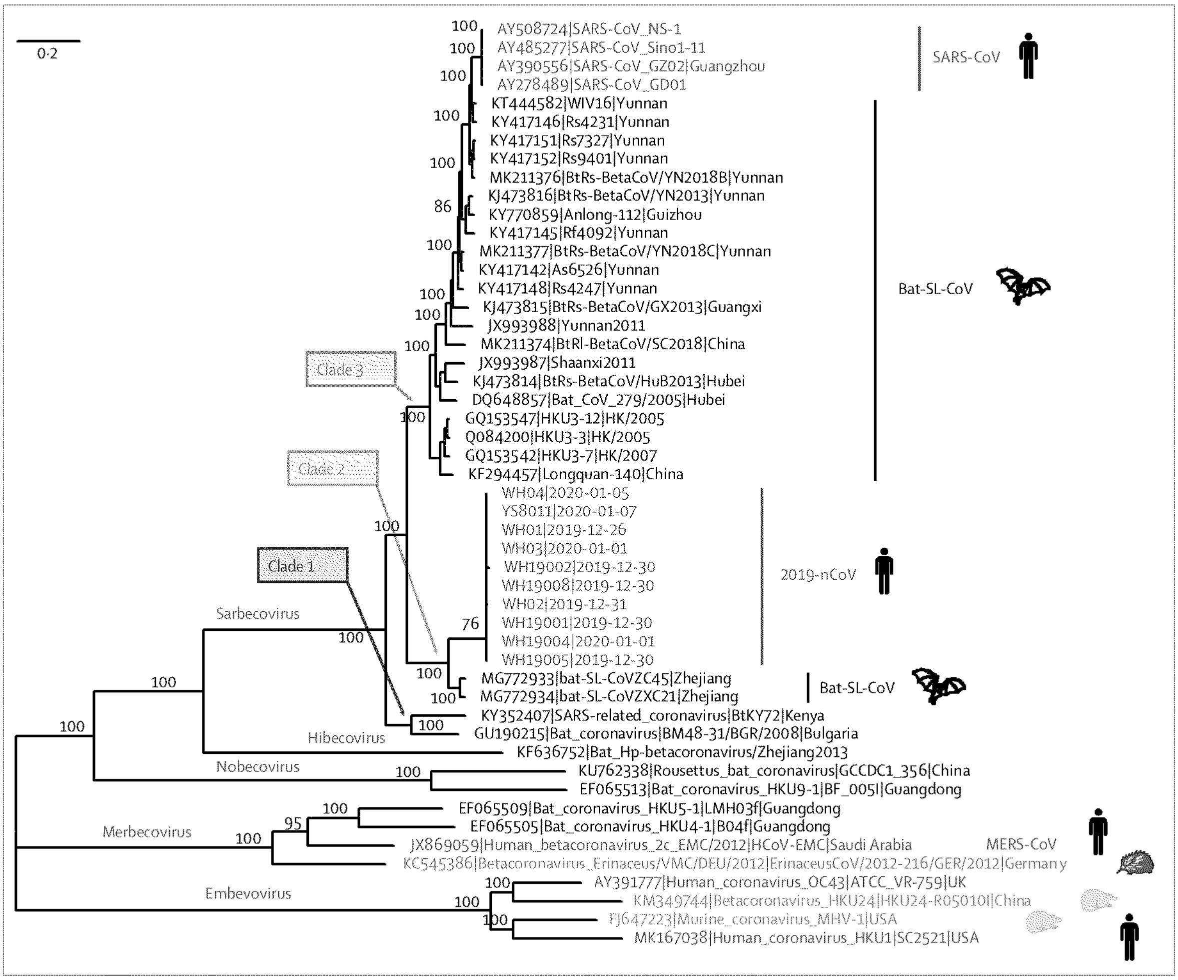

Figure 3: Phylogenetic analysis of full-length genomes of 2019-nCoV and representative viruses of the genus Betacoronavirus
2019-nCoV=2019 novel coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus.

Sarbecovirus could be classifiedinto three well supported clades: two SARS-CoV-related strains from *Rhinolophus* sp from Bulgaria (accession number GU190215) and Kenya (KY352407) formed clade 1; the ten 2019-nCoV from Wuhan and the two bat-derived SARS-like strains from Zhoushan in eastern China (bat-SL-CoVZC45 and bat-SL-CoVZXC21) formed clade 2, which was notable for the long branch separating the human and bat viruses; and SARS-CoV strains from humans and many genetically similar SARS-like coronaviruses from bats collected from southwestern China formed clade 3, with bat-derived coronaviruses also falling in the basal positions (figure 3). In addition, 2019-nCoV was distinct from SARS-CoV in a phylogeny of the complete RNA-dependent RNA polymerase (*RdRp*) gene (appendix p 2). This evidence indicates that 2019-nCoV is a novel betacoronavirus from the subgenus Sarbecovirus.

As the sequence similarity plot revealed changes in genetic distances among viruses across the 2019-nCoV genome, we did additional phylogenetic analyses of the major encoding regions of representative members of the subgenus Sarbecovirus. Consistent with the genome phylogeny, 2019-nCoV, bat-SL-CoVZC45, and bat-SL-CoVZXC21 clustered together in trees of the 1a and spike genes (appendix p 3). By contrast, 2019-nCoV did not cluster with bat-SL-CoVZC45 and bat-SL-CoVZXC21 in the 1b tree, but instead formed a distinct clade with SARS-CoV, bat-SL-CoVZC45, and bat-SL-CoVZXC21 (appendix p 3), indicative of potential recombination events in 1b, although these probably occurred in the bat coronaviruses rather than 2019-nCoV. Phylogenetic analysis of the 2019-nCoV genome excluding 1b revealed similar evolutionary relationships as the full-length viral genome (appendix p 3).

The envelope spike (S) protein mediates receptor binding and membrane fusion[24] and is crucial for determining host tropism and transmission capacity.[25,26] Generally, the spike protein of coronaviruses is functionally divided into the S1 domain (especially positions 318–510 of SARS-CoV), responsible for receptor binding,

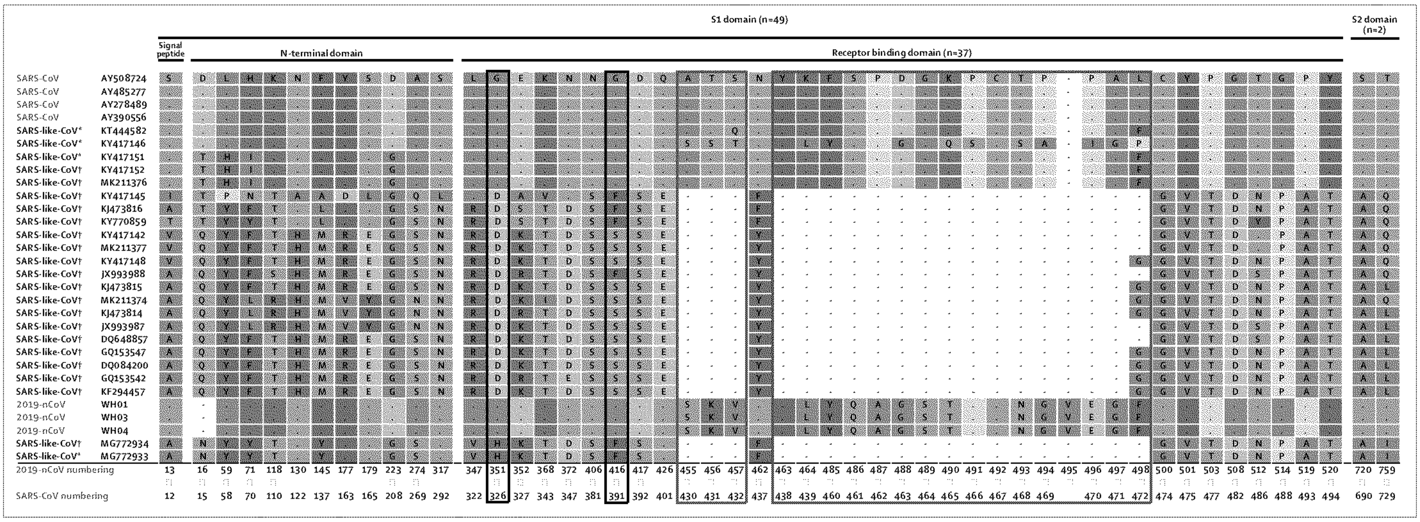

Figure 4: **Specific amino acid variations among the spike proteins of the subgenussarbecovirus**
Viruses are ordered by the tree topology (as shown in figure 3) from top to bottom. One-letter codes are used for amino acids. CoV=coronavirus. 2019-nCoV=2019 novel coronavirus. SARS=severe acute respiratory syndrome. *Bat-derived SARS-like viruses that can grow in human cell lines or in mice. †Bat-derived SARS-like viruses without experimental data available.

and the S2 domain, responsible for cell membrane fusion.[27] The 2019-nCoV S2 protein showed around 93% sequence identity with bat-SL-CoVZC45 and bat-SL-CoVZXC21—much higher than that of the S1 domain, which had only around 68% identity with these bat-derived viruses. Both the N-terminal domain and the C-terminal domain of the S1 domain can bind to host receptors.[28] We inspected amino acid variation in the spike protein among the Sarbecovirus coronaviruses (figure 4). Although 2019-nCoV and SARS-CoV fell within different clades (figure 3), they still possessed around 50 conserved amino acids in S1, whereas most of the bat-derived viruses displayed mutational differences (figure 4). Most of these positions in the C-terminal domain (figure 4). In addition, a number of deletion events, including positions 455–457, 463–464, and 485–497, were found in the bat-derived strains (fig ure 4).

The receptor-binding domain of betacoronaviruses, which directly engages the receptor, is commonly located in the C-terminal domain of S1, as in SARS-CoV[29] for lineage B, and MERS-CoV[30,31] and BatCoV HKU4,[32] for lineage C (figure 5). Through phylogenetic analysis of the receptor-binding domain of four differentlineages of betacoronaviruses (appendix p 4), we found that, although 2019-nCoV was closer to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level, the receptor-binding domain of 2019-nCoV fell within lineage B and was closer to that of SARS-CoV (figure 5A). The three-dimensional structure of 2019-nCoV receptor-binding domain was modelled using the Swiss-Model program[33] with the SARS-CoV receptor-binding domain structure (Protein Data Bank ID 2DD8)[34] as a template. This analysis suggested that, like other betacoronaviruses, the receptor-binding domain was composed of a core and an external subdomain (figure 5B–D). Notably, the external subdomain of the 2019-nCoV receptor-binding domain was more similar to that of SARS-CoV. This result suggests that 2019-nCoV might also use angiotensin-converting enzyme 2 (ACE2) as a cell receptor. However, we also observed that several key residues responsible for the binding of the SARS-CoV receptor-binding domain to the ACE2 receptor were variable in the 2019-nCoV receptor-binding domain (including Asn439, Asn501, Gln493, Gly485 and Phe486; 2019-nCoV numbering).

Discussion

From genomic surveillance of clinical samples from patients with viral pneumonia in Wuhan, China, a novel coronavirus (termed 2019-nCoV) has been identified.[10,11] Our phylogenetic analysis of 2019-nCoV, sequenced from nine patients' samples, showed that the virus belongs to the subgenus Sarbecovirus. 2019-nCoV was more similar to two bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21, than to known human-infecting coronaviruses, including the virus that caused the SARS outbreak of 2003.

Epidemiologically, eight of the nine patients in our study had a history of exposure to the Huanan seafood market in Wuhan, suggesting that they might have been in close contact with the infection source at the market. However, one patient had never visited the market, although he had stayed in a hotel near the market before the onset of their illness. This findingsuggests either possible droplet transmission or that the patient was infected by a currently unknown source. Evidence of clusters of infected family members and medical workers has now confirmed the presence of human-to-human transmission.[12] Clearly, this infection is a major public health concern, particularly as this outbreak coincides with the peak of the Chinese

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Spring Festival travel rush, during which hundreds of millions of people will travel through China.

As a typical RNA virus, the average evolutionary rate for coronaviruses is roughly 10^{-4} nucleotide substitutions per site per year,[1] with mutations arising during every replication cycle. It is, therefore, striking that the sequences of 2019-nCoV from different patients described here were almost identical, with greater than 99·9% sequence identity. This finding suggests that 2019-nCoV originated from one source within a very short period and was detected relatively rapidly. However, as the virus transmits to more individuals, constant surveillance of mutations arising is needed.

Phylogenetic analysis showed that bat-derived coronaviruses fell within all five subgenera of the genus Betacoronavirus. Moreover, bat-derived coronaviruses fell in basal positions in the subgenus Sarbecovirus, with 2019-nCoV most closely related to bat-SL-CoVZC45 and bat-SL-CoVZXC21, which were also sampled from bats.[23] These data are consistent with a bat reservoir for coronaviruses in general and for 2019-nCoV in particular. However, despite the importance of bats, several facts suggest that another animal is acting as an intermediate host between bats and humans. First, the outbreak was first reported in late Dece mber, 2019, when most bat species in Wuhan are hibernating. Second, no bats were sold or found at the Huanan seafood market, whereas various non-aquatic animals (including mammals) were available for purchase. Third, the sequence identity between 2019-nCoV and its close relatives bat-SL-CoVZC45 and bat-SL-CoVZXC21 was less than 90%, which is reflected in the relatively long branch between them. Hence, bat-SL-CoVZC45 and bat-SL-CoVZXC21 are not direct ancestors of 2019-nCoV. Fourth, in both SARS-CoV and MERS-CoV, bats acted as the natural reservoir, with another animal (masked palm civet for SARS-CoV[35] and dromedary camels for MERS-CoV)[36] acting as an intermediate host, with humans as terminal hosts. Therefore, on the basis of current data, it seems likely that the 2019-nCoV causing the Wuhan outbreak might also be initially hosted by bats, and might have been transmitted to humans via currently unknown wild animal(s) sold at the Huanan seafood market.

Previous studies have uncovered several receptors that different coronaviruses bind to, such as ACE2 for SARS-CoV[29] and CD26 for MERS-CoV.[30] Our molecular modelling showed structural similarity between the receptor-binding domains of SARS-CoV and 2019-nCoV. Therefore, we suggest that 2019-nCoV might use ACE2 as the receptor, despite the presence of amino acid mutations in the 2019-nCoV receptor-binding domain. Although a previous study using HeLa cells expressing ACE2 proteins showed that 2019-nCoV could employ the ACE2 receptor,[37] whether these mutations affectACE2 binding or change receptor tropism requires further study.

Recombination has been seen frequently in coronaviruses.[1] As expected, we detected recombination in the Sarbecoviruses analysed here. Our results suggest that recombination events are complex and are more likely occurring in bat coronaviruses than in 2019-nCoV. Hence, despite its occurrence, recombination is probably not the reason for emergence of this virus, although this inference might change if more closely related animal viruses are identified.

In conclusion, we have described the genomic structure of a seventh human coronavirus that can cause severe pneumonia and have shed light on its origin and

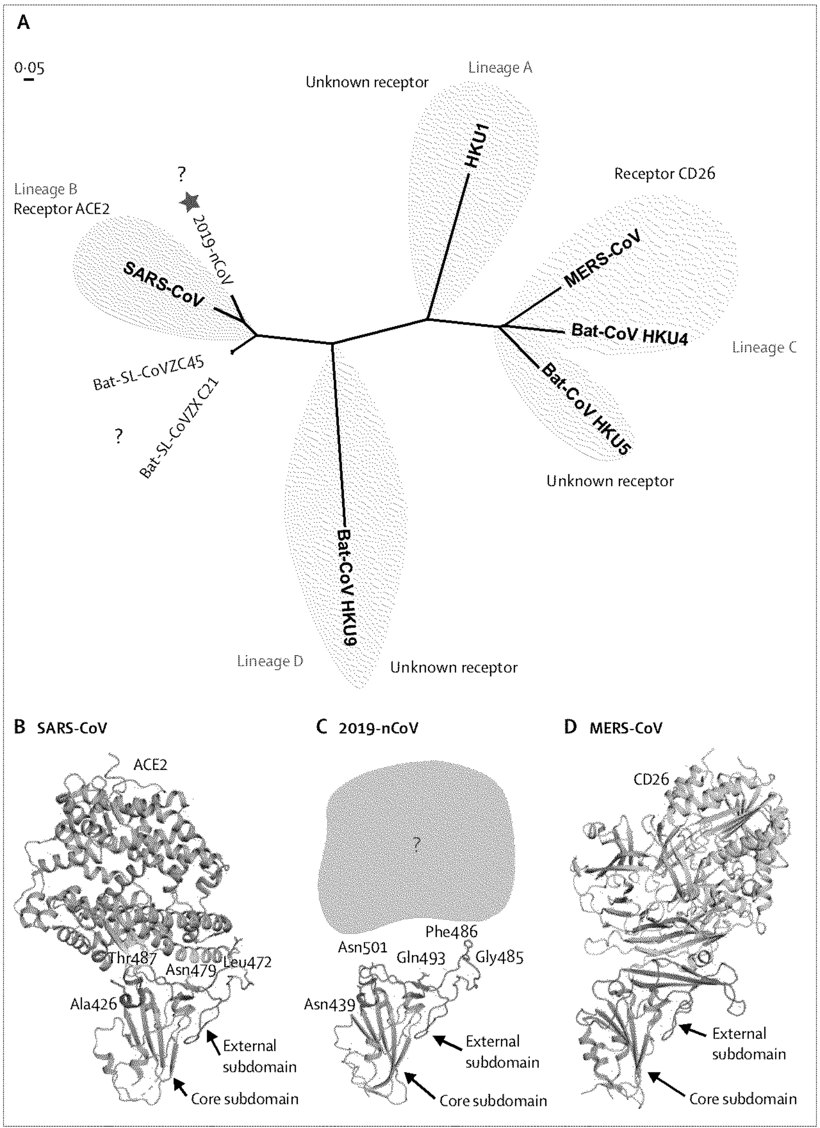

Figure 5: **Phylogenetic analysis and homology modelling of the receptor-binding domain of the 2019-nCoV, SARS-CoV, and MERS-CoV**

(A) Phylogenetic analysis of the receptor-binding domain from various betacoronaviruses. The star highlights 2019-nCoV and the question marks means that the receptor used by the viruses remains unknown. Structural comparison of the receptor-binding domain of SARS-CoV (B), 2019-nCoV (C), and MERS-CoV (D) binding to their own receptors. Core subdomains are magenta, and the external subdomains of SARS-CoV, 2019-nCoV, and MERS CoV are orange, dark blue, and green, respectively. Variable residues between SARS-CoV and 2019-nCoV in the receptor-binding site are highlighted as sticks. CoV=coronavirus. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS=Middle East respiratory syndrome coronavirus.

receptor-binding properties. More generally, the disease outbreak linked to 2019-nCoV again highlights the hidden virus reservoir in wild animals and their potential to occasionally spill over into human populations.

Contributors

GFG, WT, WS, WC, WX, and GW designed the study. RL, XZ, PN, HW, WW, BH, NZ, XM, WZ, LZ, JC, YM, JW, YL, JY, ZX, JM, WJL, and DW did the experiments. BY, FZ, and ZH provided samples. WS, WC, WT, JL, HS, YB, LW, TH, and HZ analysed data. WS, WT, and JL wrote the report. ECH and GFG revised the report.

Declaration of interests

We declare no competing interests.

Data sharing

Data are available on various websites and have been made publicly available (more information can be found in the first paragraph of the Results section).

Acknowledgments

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To: Shore, Carolyn[CShore@nas.edu]; Peter Daszak[daszak@ecohealthalliance.org]; 'Chakravarti, Aravinda'[Aravinda.Chakravarti@nyulangone.org]; Kristian Andersen ; Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]
Cc: Chao, Samantha[SChao@nas.edu]; Pope, Andrew[APope@nas.edu]
From: Baric, Ralph S[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB0D9CC80C184735A4E862C3BDD8A15D-RALPH S BAR]
Sent: Tue 2/4/2020 12:51:50 PM (UTC-05:00)
Subject: RE: URGENT: Please review by NOON if at all possible...
s41586-020-2012-7_reference.pdf

This is the right paper. Ralph

From: Shore, Carolyn <CShore@nas.edu>
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Cc: Chao, Samantha <SChao@nas.edu>; Pope, Andrew <APope@nas.edu>
Subject: RE: URGENT: Please review by NOON if at all possible...

Thank you, all, for your input on the draft letter. A couple of clarifying questions regarding citations:

- Ralph – is the attached article the appropriate citation for your comment regarding the closest relative of 2019-nCoV or is there another citation we should reference?
- Are there any other articles that we should cite that examine the origin of 2019-nCoV specifically?

Best,
Carolyn

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, February 4, 2020 12:01 PM
To: Pope, Andrew <APope@nas.edu>; 'Chakravarti, Aravinda' <Aravinda.Chakravarti@nyulangone.org>; Kristian Andersen ; Ralph Baric (rbaric@email.unc.edu) <rbaric@email.unc.edu>; Trevor Bedford (trevor@bedford.io) <trevor@bedford.io>; Gigi Gronvall <ggronvall@jhu.edu>; Tom Inglesby (tinglesby@jhu.edu) <tinglesby@jhu.edu>; Stanley Perlman (stanley-perlman@uiowa.edu) <stanley-perlman@uiowa.edu>
Cc: Shore, Carolyn <CShore@nas.edu>; Chao, Samantha <SChao@nas.edu>
Subject: RE: URGENT: Please review by NOON if at all possible...
Importance: High

I agree with all of the other comments so far sent in, and want to add the following:

1) In the 3rd paragraph, it's important to add "including further samples from wildlife", and perhaps the rationale for this "to identify other viruses closely related to nCoV"
2) Re. references for #3 that there are current and planned studies underway on the bat origins of CoVs. Here are some references to pick from if they make sense:

- Latinne A, Hu B, Olival KJ, et al.; Origin and cross-species transmission of bat coronaviruses in China. *Nature Communications* 2020;**In review**.
- Wang N, Li S-Y, Yang X-L, et al.; Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China. *Virologica Sinica* 2018. doi: 10.1007/s12250-018-0012-7.
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Cheers,

Peter

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EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

From: Pope, Andrew [mailto:APope@nas.edu]
Sent: Tuesday, February 4, 2020 9:11 AM
To: 'Chakravarti, Aravinda'; Kristian Andersen ; Ralph Baric (rbaric@email.unc.edu); Trevor Bedford (trevor@bedford.io); Peter Daszak; Gigi Gronvall; Tom Inglesby (tinglesby@jhu.edu); Stanley Perlman (stanley-perlman@uiowa.edu)
Cc: Shore, Carolyn; Chao, Samantha
Subject: URGENT: Please review by NOON if at all possible...
Importance: High

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a “Based on Science” web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the data needs that are identified. We think it would be helpful to be a bit more specific, but don’t want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

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nature

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Accelerated Article Preview

A pneumonia outbreak associated with a new coronavirus of probable bat origin

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Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Xu-Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Geng-Fu Xiao & Zheng-Li Shi

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ACCELERATED ARTICLE PREVIEW

Article

A pneumonia outbreak associated with a new coronavirus of probable bat origin

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Peng Zhou[1,5], Xing-Lou Yang[1,5], Xian-Guang Wang[2,5], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]*

Since the SARS outbreak 18 years ago, a large number of severe acute respiratory syndrome-related coronaviruses (SARSr-CoV) have been discovered in their natural reservoir host, bats[1–4]. Previous studies indicated that some of those bat SARSr-CoVs have the potential to infect humans[5–7]. Here we report the identification and characterization of a novel coronavirus (2019-nCoV) which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started from 12 December 2019, has caused 2,050 laboratory-confirmed infections with 56 fatal cases by 26 January 2020. Full-length genome sequences were obtained from five patients at the early stage of the outbreak. They are almost identical to each other and share 79.5% sequence identify to SARS-CoV. Furthermore, it was found that 2019-nCoV is 96% identical at the whole genome level to a bat coronavirus. The pairwise protein sequence analysis of seven conserved non-structural proteins show that this virus belongs to the species of SARSr-CoV. The 2019-nCoV virus was then isolated from the bronchoalveolar lavage fluid of a critically ill patient, which can be neutralized by sera from several patients. Importantly, we have confirmed that this novel CoV uses the same cell entry receptor, ACE2, as SARS-CoV.

ACCELERATED ARTICLE PREVIEW

Coronavirus has caused two large-scale pandemic in the last two decades, SARS and MERS (Middle East respiratory syndrome)[8,9]. It was generally believed that SARSr-CoV, mainly found in bats, might cause future disease outbreak[10,11]. Here we report on a series of unidentified pneumonia disease outbreaks in Wuhan, Hubei province, central China. Started from a local seafood market, the outbreak has grown substantial to infect 2050 people in China with 56 deaths and to infect 35 people in 11 other countries up to January 26, 2020[12]. Typical clinical symptoms of these patients are fever, dry cough, dyspnea, headache, and pneumonia. Disease onset may result in progressive respiratory failure due to alveolar damage (as observed by transverse chest CT images) and even death. The disease was determined as viral induced pneumonia by clinicians according to clinical symptoms and other criteria including body temperature rising, lymphocytes and white blood cells decreasing (sometimes normal for the later), new pulmonary infiltrates on chest radiography, and no obvious improvement upon three days antibiotics treatment. It appears most of the early cases had contact history with the original seafood market, but the disease progressed to human-to-human transmission now.

Samples from seven patients with severe pneumonia (six are seafood market sellers or delivers), who were enrolled in intensive unit cares at the beginning of the outbreak, were sent to WIV laboratory for pathogen diagnosis (Extended Data Table 1). As a CoV lab, we first used pan-CoV PCR primers to test these samples[13], considering the outbreak happened in winter and in a market, same environment as SARS. We found five PCR positive. A sample (WIV04) collected from bronchoalveolar lavage fluid (BALF) was analysed by metagenomics analysis using next-generation sequencing (NGS) to identify potential etiological agents. Of the 10,038,758 total reads, or 1582 total reads obtained after human genome filtering, 1378 (87.1%) matched sequences of SARSr-CoV (Fig. 1a). By *de novo* assembly and targeted PCR, we obtained a 29,891-bp CoV genome that shared 79.5% sequence identity to SARS-CoV BJ01 (GenBank accession number AY278488.2). High genome coverage was obtained by remapping the total reads to this genome (Extended Data Figure 1). This sequence has been submitted to GISAID (accession no. EPI_ISL_402124). Following the name by WHO, we tentatively call it novel coronavirus 2019 (2019-nCoV). Four more full-length genome sequences of 2019-nCoV (WIV02, WIV05, WIV06, and WIV07) (GISAID accession nos. EPI_ISL_402127-402130) that were above 99.9% identical to each other were subsequently obtained from other four patients using NGS and PCR (Extended Data Table 2).

The virus genome consists of six major open reading frames (ORFs) common to coronaviruses and a number of other accessory genes (Fig. 1b). Further analysis indicates that some of the 2019-nCoV genes shared less than 80% nt sequence identity to SARS-CoV. However, the seven conserved replicase domains in ORF1ab that were used for

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CoV species classification, are 94.6% aa sequence identical between 2019-nCoV and SARS-CoV, implying the two belong to same species (Extended Data Table 3).

We then found a short RdRp region from a bat coronavirus termed BatCoV RaTG13 which we previously detected in *Rhinolophus affinis* from Yunnan Province showed high sequence identity to 2019-nCoV. We did full-length sequencing to this RNA sample (GISAID accession no.EPI_ISL_402131). Simplot analysis showed that 2019-nCoV was highly similar throughout the genome to RaTG13 (Fig. 1c), with 96.2% overall genome sequence identity. Using the aligned genome sequences of 2019-nCoV, RaTG13, SARS-CoV and previously reported bat SARSr-CoVs, no evidence for recombination events was detected in the genome of 2019-nCoV. The phylogenetic analysis of full-length genome, RNA-dependent RNA polymerase (RdRp) gene and S gene sequences all showed that RaTG13 is the closest relative of the 2019-nCoV and form a distinct lineage from other SARSr-CoVs (Fig. 1d and Extended Data Figure 2). The receptor binding protein spike (S) gene was highly divergent to other CoVs (Extended Data Figure 2), with less than 75% nt sequence identity to all previously described SARSr-CoVs except a 93.1% nt identity to RaTG13 (Extended Data Table 3). The S genes of 2019-nCoV and RaTG13 S gene are longer than other SARSr-CoVs. The major differences in 2019-nCoV are the three short insertions in the N-terminal domain, and four out of five key residues changes in the receptor-binding motif, in comparison with SARS-CoV (Extended Data Figure 3). Whether the insertions in N-terminal domain of 2019-nCoV confers a sialic acid binding activity like MERS-CoV needs to be further studied. The close phylogenetic relationship to RaTG13 provides evidence for a bat origin of 2019-nCoV.

We rapidly developed a qPCR detection based on the receptor-binding domain of spike gene, the most variable region among genome (Fig. 1c). Our data show the primers could differentiate 2019-nCoV with all other human coronaviruses including bat SARSr-CoV WIV1, which is 95% identity to SARS-CoV (Extended Data Figure 4a and 4b). From the seven patients, we found 2019-nCoV positive in six BALF and five oral swab samples during the first sampling by qPCR and conventional PCR. However, we can no longer find viral positive in oral swabs, anal swabs, and blood from these patients during the second sampling (Fig. 2a). We have to point out that other qPCR targets including RdRp or E gene may be suggested for routine detection. Based on these findings, we presume that the disease should be transmitted through airway, yet we can't rule out other possibilities if the investigation extended to include more patients.

For serological detection of 2019-nCoV, we used previously developed bat SARSr-CoV Rp3 nucleocapsid protein (NP) as antigen in IgG and IgM ELISA test, which shared 92% amino acid identity to 2019-nCoV NP (Extended Data Figure 5) and showed no cross-reactivity against other human coronaviruses except SARSr-CoV[7]. As a research lab, we were only able to get five serum samples from the seven viral infected patients. We monitored viral antibody levels in one patient (ICU-06) at seven, eight, nine and eighteen days after disease onset (Extended Data Table 2). A clear trend of IgG and IgM titre (decreased at the last day) increase was observed (Fig. 2b). For a second investigation, we tested viral antibody for five of the seven viral positive patients around twenty days after disease onset (Extended Data Table 1 and 2). All patient samples, but not samples from healthy people, showed strong viral IgG positive (Fig. 2b). We also found three IgM positive, indicating acute infection.

We then successfully isolated the virus (named 2019-nCoV BetaCoV/Wuhan/WIV04/2019), in both Vero and Huh7 cells using BALF sample from ICU-06 patient. Clear cytopathogenic effects were observed in cells after three days incubation (Extended Data Figure 6a and 6b). The identity of the strain WIV04 was verified in Vero E6 cells by immunofluorescence microscopy using cross-reactive viral NP antibody (Extended Data Figure 6c and 6d), and by metagenomic sequencing, from which most of the reads mapped to 2019-nCoV and qPCR showing viral load increase from day 1 to day 3 (Extended Data Figure 6e and 6f). Viral particles in ultrathin sections of infected cells displayed typical coronavirus morphology under electron microscopy (Extended Data Figure 6g). To further confirm the neutralization activity of the viral IgG positive samples, we conducted serum-neutralization assays in Vero E6 cells using the five IgG positive patient sera. We demonstrate that all samples were able to neutralize 120 TCID50 2019-nCoV at a dilution of 1:40-1:80. We also show that this virus could be cross-neutralized by horse anti-SARS-CoV serum (offered by L-F Wang) at dilutions 1:80, but the potential for cross reactivity with SARS-CoV antibodies needs to be confirmed with anti-SARS-CoV serum from humans (Extended Data Table 4).

Angiotensin converting enzyme II (ACE2) was known as cell receptor for SARS-CoV[14]. To determine whether 2019-nCoV also use ACE2 as a cellular entry receptor, we conducted virus infectivity studies using HeLa cells expressing or not expressing ACE2 proteins from humans, Chinese horseshoe bats, civet, pig, and mouse. We show that 2019-nCoV is able to use all but mouse ACE2 as an entry receptor in the ACE2-expressing cells, but not cells without ACE2, indicating which is likely the cell receptor of 2019-nCoV (Fig. 3). We also proved that 2019-nCoV does not use other coronavirus receptors, aminopeptidase N and dipeptidyl peptidase 4 (Extended Data Figure 7).

The study provides the first detailed report on 2019-nCoV, the likely etiology agent responsible for ongoing acute respiratory syndrome epidemic in Wuhan, Central China. Viral specific nucleotide positive and viral protein seroconversion observed in all patients tested provides evidence of an association between the disease and the presence of this virus. However, there are still many urgent questions to be answered. The association between the 2019-nCoV and the disease has not been proved by animal experiments to full the Koch postulates. We don't know the transmission routine of this virus among hosts yet. It seems the virus is becoming more transmissible between human-to-human. We should closely monitor if the virus continue evolving to become more virulent. Owing to shortage of specific treatment and considering the relatedness between SARS-CoV and 2019-nCoV, some drugs and pre-clinical vaccine against SARS-CoV probably can be applied to this virus. Finally, considering the wide spread of SARSr-CoV in their natural reservoirs, future research should be focused on active surveillance of these viruses through a broader geographic regions. In the long-term, broad-spectrum antiviral drugs and vaccine should be prepared for the future emerging infectious diseases caused by this cluster of virus. Most importantly, strict regulations against the wildlife domestication and consuming should be implemented.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2012-7

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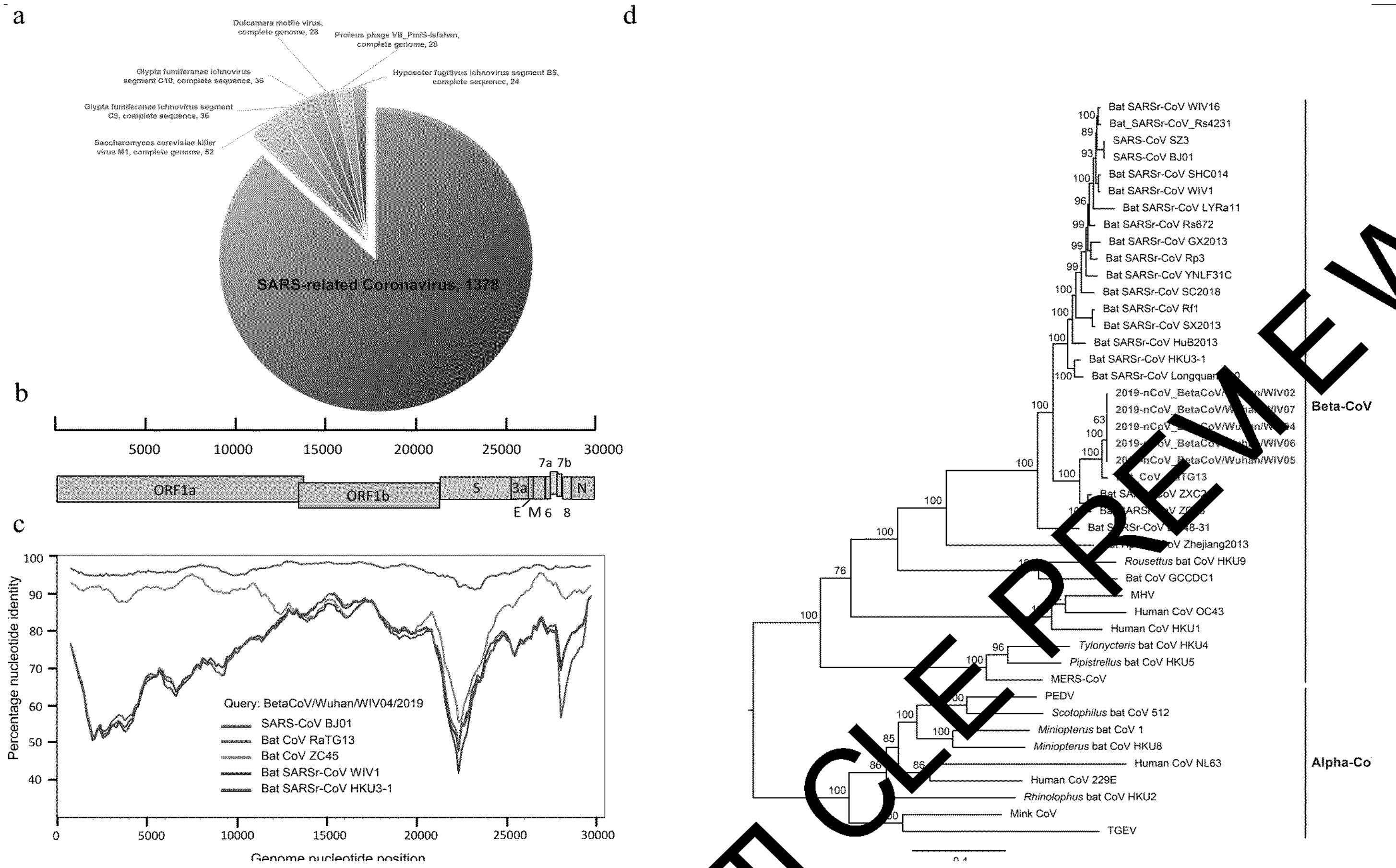

Fig. 1 | Genome characterization of 2019-nCoV. a, pie chart showing metagenomics analysis of next-generation sequencing of bronchoalveolar lavage fluid from patient ICU06. **b**, Genomic organization of 2019-nCoV WIV04. **c**, Similarity plot based on the full-length genome sequence of 2019-nCoV WIV04. Full-length genome sequences of SARS-CoV BJ01, bat SARSr-CoV WIV1, bat coronavirus RaTG13 and ZC45 were used as reference sequences. **d**, Phylogenetic tree based on nucleotide sequences of complete genomes of coronaviruses. Software used and settings can be found in material and method section.

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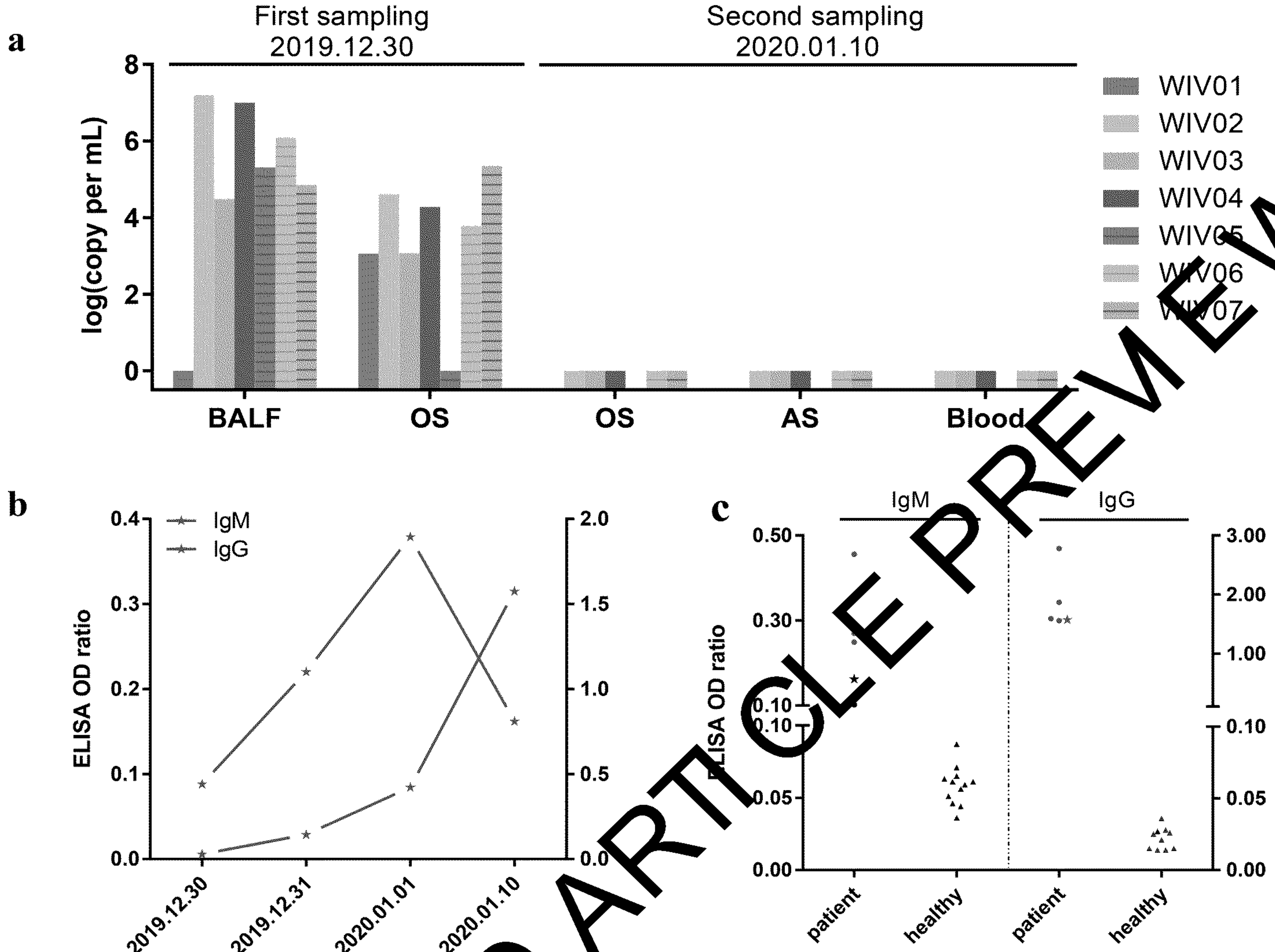

Fig. 2 | Molecular and serological investigation of patient samples. **a**, molecular detection of 2019-nCoV in seven patients during two times of sampling. Patient information can be found in Extended Data Table 1 and 2. Details on detection method can be found in material and methods. BALF, bronchoalveolar lavage fluid; OS, oral swab; AS, anal swab. **b**, dynamics of 2019-nCoV antibodies in one patient who showed sign of disease on 2019.12.23 (ICU-06). **c**, serological test of 2019-nCoV antibodies in five patients (more information can be found in Extended Data Table 2). Star indicates data collected from patient ICU-06 on 2020.01.10. For b and c, cut-off was set up as 0.2 for IgM test and 0.3 for IgG test, according to healthy controls.

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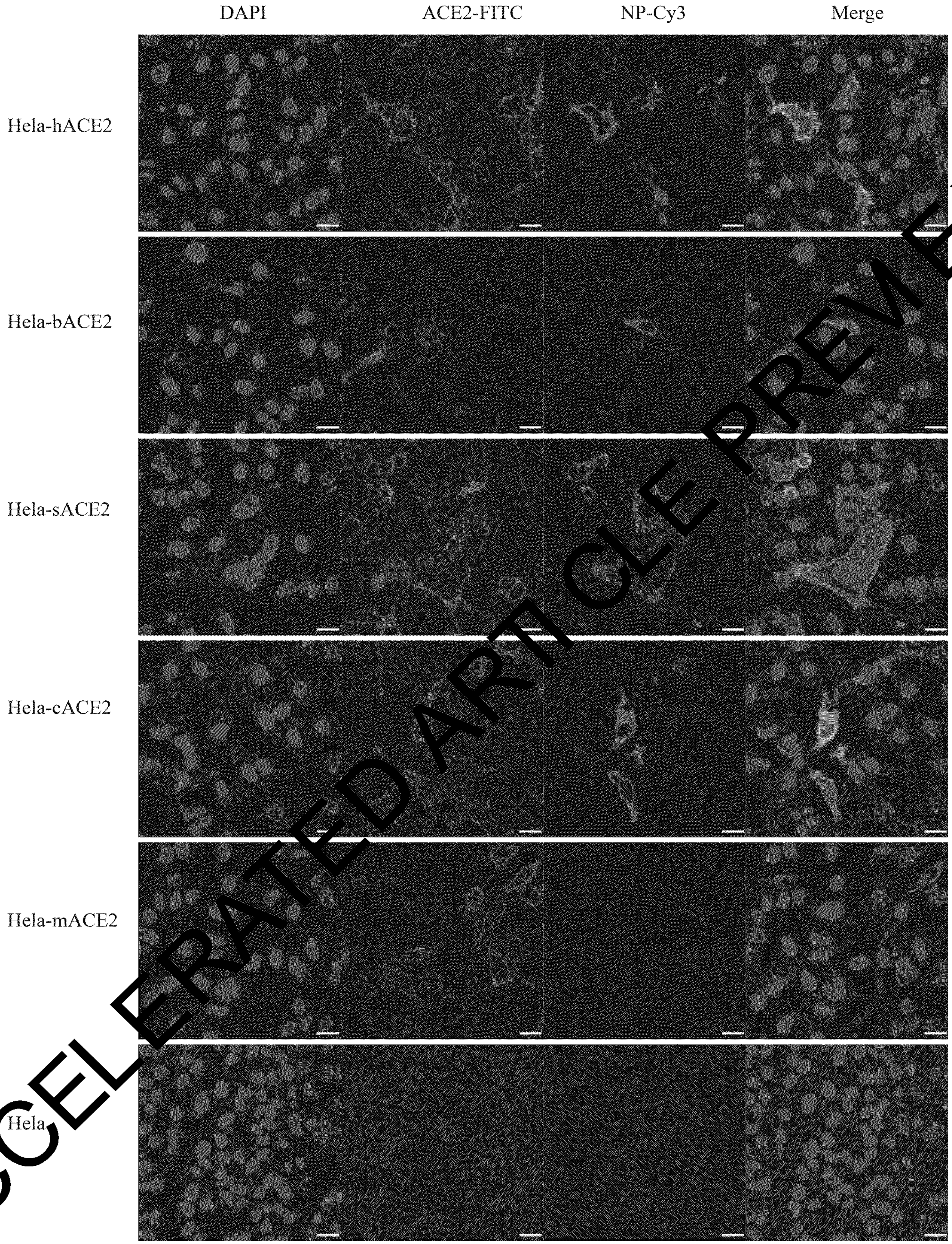

Fig. 3 | Analysis of 2019-nCoV receptor usage. Determination of virus infectivity in HeLa cells with or without the expression of ACE2. h, human; b, *Rhinolophus sinicus* bat; c, civet; s, swine (pig); m, mouse. ACE2 protein (green), viral protein (red) and nuclei (blue) was shown. Scale bar=10 um.

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Methods

Sample collection

Human samples, including oral swabs, anal swabs, blood, and BALF samples were collected by Jinyintan hospital (Wuhan) with the consent from all patients and approved by the ethics commission of the designated hospital for emerging infectious diseases. Patients were sampled without gender or age preference unless where indicated. For swabs, 1.5 ml DMEM+2% FBS medium was added each tube. Supernatant was collected after 2500 rpm, 60 s vortex and 15-30 min standing. Supernatant from swabs or BALF (no pretreatment) was added to either lysis buffer for RNA extraction or to viral transport medium (VTM) for virus isolation. VTM composed of Hank's balanced salt solution at pH7.4 containing BSA (1%), amphotericin (15 μg/ml), penicillin G (100 units/ml), and streptomycin (50 μg/ml). Serum was separated by centrifugation at 3,000 *g* for 15 min within 24 h of collection, followed by 56 ^{0}C 30 min inactivation, and then stored at 4 ^{0}C until use.

Virus isolation, cell infection, electron microscope and neutralization assay

The following cells were used for virus isolation in this study: Vero, Vero E6, and Huh7 that were cultured in DMEM +10% FBS. A list of cells were used for susceptibility test (Extended Data Fig. 6). All cell lines were tested free of mycoplasma contamination, applied to species identification and authenticated by microscopic morphologic evaluation. None of cell lines was on the list of commonly misidentified cell lines (by ICLAC).

Cultured cell monolayers were maintained in their respective medium. PCR-positive BALF sample from ICU-06 patient was spin at 8,000 g for 15 min, filtered and diluted 1:2 with DMEM supplied with 16 μg/ml trypsin before adding to cells. After incubation at 37 ^{0}C for 1 h, the inoculum was removed and replaced with fresh culture medium containing antibiotics (below) and 16 μg/ml trypsin. The cells were incubated at 37 ^{0}C and observed daily for cytopathic effect (CPE). The culture supernatant was examined for presence of virus by qRT-PCR developed in this study, and cells were examined by immunofluorescent using SARSr-CoV Rp3 NP antibody made in house (1:100). Penicillin (100 units/ml) and streptomycin (15 μg/ml) were included in all tissue culture media.

The Vero E6 cells were infected with new virus at MOI of 0.5 and harvested 48 hpi. Cells were fixed with 2.5% (wt/vol) glutaraldehyde and 1% osmium tetroxide, and then dehydrated through a graded series of ethanol concentrations (from 30 to 100%), and embedded with epoxy resin. Ultrathin sections (80 nm) of embedded cells were prepared, deposited onto Formvar-coated copper grids (200 mesh), stained with uranyl acetate and lead citrate, then observed under 200 kV Tecnai G2 electron microscope.

The virus neutralization test was carried out in a 48-well plate. The patient serum samples were heat-inactivated by incubation at 56 ^{0}C for 30 min before use. The serum samples (5 μL) were diluted to 1:10, 1:20, 1:40 or 1:80, and then an equal volume of virus stock was added and incubated at 37 ^{0}C for 60 min in a 5% CO_2 incubator. Diluted horse anti SARS-CoV serum or serum samples from healthy people were used as control. After incubation, 100 μL mixtures were inoculated onto monolayer Vero E6 cells in a 48-well plate for 1 hour. Each serum were repeated triplicate. After removing the supernatant, the plate was washed twice with DMEM medium. Cells were incubated with DMEM supplemented with 2% FBS for 24 hours. Then the cells were fixed with 4% formaldehyde. And the virus were detected using SL-CoV Rp3 NP antibody followed by Cy3-conjugated mouse anti-rabbit IgG. Nuclei were stained with DAPI. Infected cell number was counted by high-content cytometers.

RNA extraction and PCR

Whenever commercial kits were used, manufacturer's instructions were followed without modification. RNA was extracted from 200 μl of samples with the High Pure Viral RNA Kit (Roche). RNA was eluted in 50 μl of elution buffer and used as the template for RT-PCR.

For qPCR analysis, primers based on 2019-nCoV S gene was designed: RBD-qF1: 5′-CAATGGTTTAACAGGCACAGG-3′; RBD-qR1: 5′-CTCAAGTGTCTGTGGATCACG-3′.RNA extracted from above used in qPCR by HiScript® II One Step qRT-PCR SYBR® Green Kit (Vazyme Biotech Co.,Ltd). Conventional PCR test was also performed using the following primer pairs: ND-CoVs-951F TGTKAGRTTYCCTAAYATTAC; ND-CoVs-1805R ACATCYTGATANARAACAGC[13]. The 20 μl qPCR reaction mix contained 10 μl 2× One Step SYBR Green Mix, 1 μl One Step SYBR Green Enzyme Mix, 0.4 μl 50 × ROX Reference Dye 1, 0.4 μl of each primer (10 uM) and 2 μl template RNA. Amplification was performed as follows: 50 ^{0}C for 3 min, 95 ^{0}C for 30 s followed by 40 cycles consisting of 95 ^{0}C for 10 s, 60 ^{0}C for 30 s, and a default melting curve step in an ABI 7700 machine.

Serological test

In-house anti-SARSr-CoV IgG and IgM ELISA kits were developed using SARSr-CoV Rp3 NP as antigen, which shared above 90% amino acid identity to all SARSr-CoVs[2]. For IgG test, MaxiSorp Nunc-immuno 96 well ELISA plates were coated (100 ng/well) overnight with recombinant NP. Human sera were used at 1:20 dilution for 1 h at 37 ^{0}C. An anti-Human IgG-HRP conjugated monoclonal antibody (Kyab Biotech Co., Ltd, Wuhan, China) was used at a dilution of 1:40000. The OD value (450–630) was calculated. For IgM test, MaxiSorp Nunc-immuno 96 well ELISA plates were coated (500 ng/well) overnight with anti-human IgM (μ chain). Human sera were used at 1:100 dilution for 40 min at 37 ^{0}C, followed by anti-Rp3 NP-HRP conjugated (Kyab Biotech Co., Ltd, Wuhan, China) at a dilution of 1:4000. The OD value (450–630) was calculated.

Examination of ACE2 receptor for 2019-nCoV infection

HeLa cells transiently expressing ACE2 were prepared by a lipofectamine 3000 system (Thermo Fisher Scientific) in 96-well plate, with mock-transfected cells as controls. 2019-nCoV grown from Vero E6 cells was used for infection at multiplicity of infection 0.05. Same for testing of APN and DPP4. The inoculum was removed after 1 h absorption and washed twice with PBS and supplemented with medium. At 24 hpi, cells were washed with PBS and fixed with 4% formaldehyde in PBS (pH 7.4) for 20 min at room temperature. ACE2 expression was detected using mouse anti-S tag monoclonal antibody followed by FITC-labelled goat anti-mouse IgG H&L (Abcam, ab96879). Viral replication was detected using rabbit antibody against the Rp3 NP protein (made in house, 1:100) followed by cyanin 3-conjugated goat anti-rabbit IgG (1:50, Abcam, ab6939). Nucleus was stained with DAPI (Beyotime). Staining patterns were examined using the FV1200 confocal microscopy (Olympus).

High throughput sequencing, pathogen screening and genome assembly

Samples from patient BALF or from virus culture supernatant were used for RNA extraction and next-generation sequencing using BGI MGISEQ2000 and Illumina MiSeq 3000 sequencers. Metagenomic analysis was carried out mainly base on the bioinformatics platform MGmapper (PE_2.24 and SE_2.24). The raw NGS reads were firstly processed by Cutadapt (v1.18) with minimum read length of 30bp. BWA (v0.7.12-r1039) was utilized to align reads to local database with a filter hits parameter at 0.8 FMM value and minimum alignment score at 30. Parameters for post-processing of assigned reads was set with minimum size normalized abundance at 0.01, minimum read count at 20 and other default parameters. A local nucleic acid database for human and mammals was employed to filter reads of host genomes before mapping reads to virus database. The results of metagenomic analysis were displayed through pie charts using WPS Office 2010. NGS reads were assembled into genomes using Geneious (v11.0.3) and

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MEGAHIT (v1.2.9). PCR and Sanger sequencing was performed to fill gaps in the genome. 5′-RACE was performed to determine the 5′-end of the genomes using SMARTer RACE 5′/3′ Kit (Takara). Genomes were annotated using Clone Manager Professional Suite 8 (Sci-Ed Software).

Phylogenetic analysis

Routine sequence management and analysis was carried out using DNAStar. The sequence alignment of complete genome sequences was performed by MAFFT (version 7.307) with default parameters. The codon alignments of full-length S and RdRp gene sequences were converted from the corresponding protein alignments by PAL2NAL (version 14), respectively, of which the protein alignments were created by Clustal Omega (version 1.2.4) under default parameters. Maximum Likelihood phylogenetic trees were carried out using RAxML (version 0.9.0) with GTR+G substitution model and 1000 bootstrap replicates.

Data availability

Sequence data that support the findings of this study have been deposited in GISAID with the accession numbers EPI_ISL_402124, EPI_ISL_402127–EPI_ISL_402130and EPI_ISL_402131.

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Author contributions Z.L.S., P.Z., Y.Y.W., and G.F.X. conceived the study. G.S.W., C.L.H., H.D.C., F.D., Q.J.C., F.X.Z., and LLL., collected patient samples. X.L.Y., B.Y., W.Z., B.L., J.C., X.S.Z., Y.L., H.G., R.D.J., M.Q.L., Y. Chen, X.W., X.R.S., and K.Z. performed qPCR, serology, and virus culturing. L.Z., Y.Z., H.R.S., and B.H. performed genome sequencing and annotations.

Competing interests The authors declare no competing interests.

Additional information

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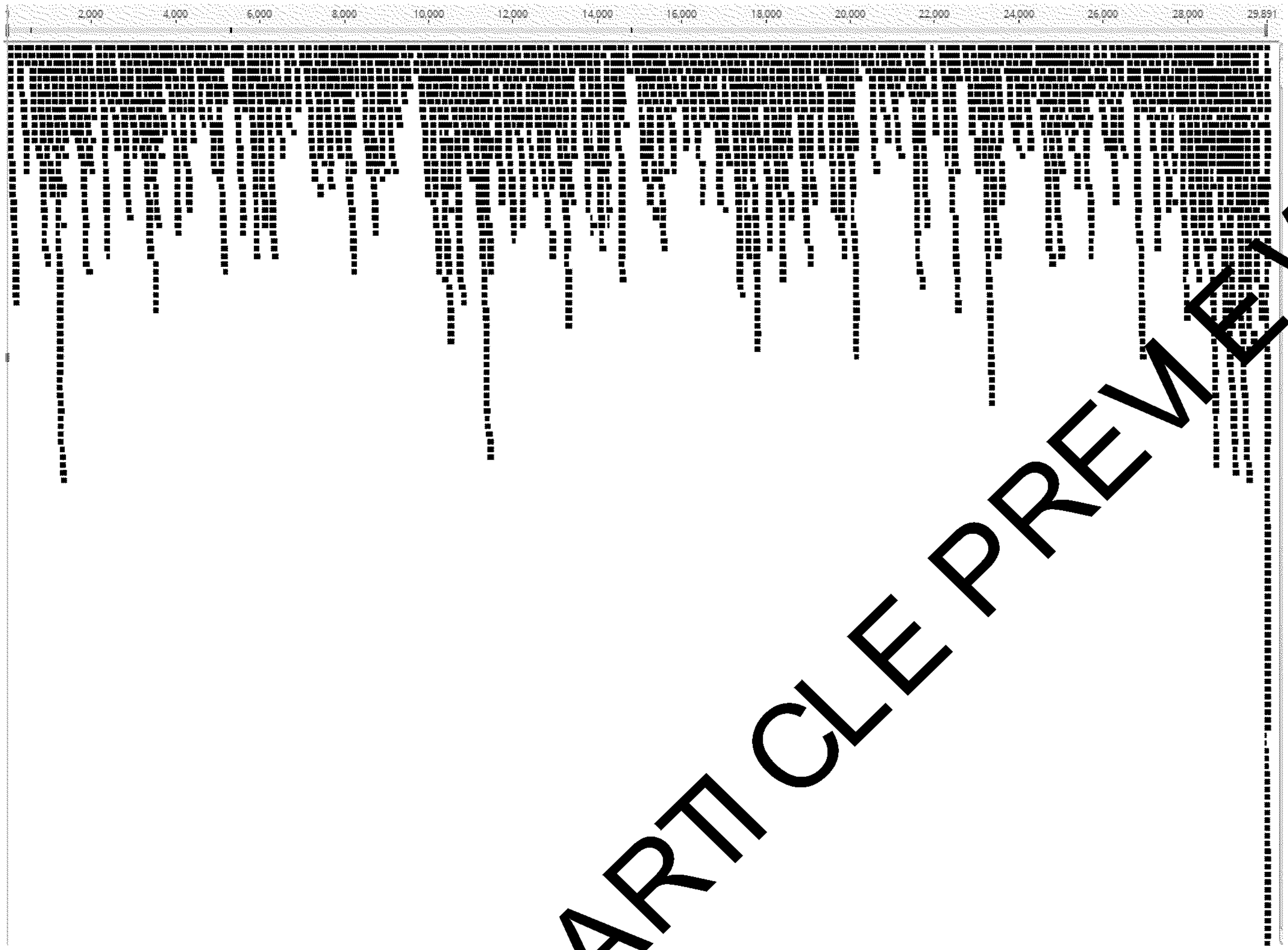

Extended Data Fig. 1 | NGS raw reads from WIV04 patient mapping to 2019-nCoV.

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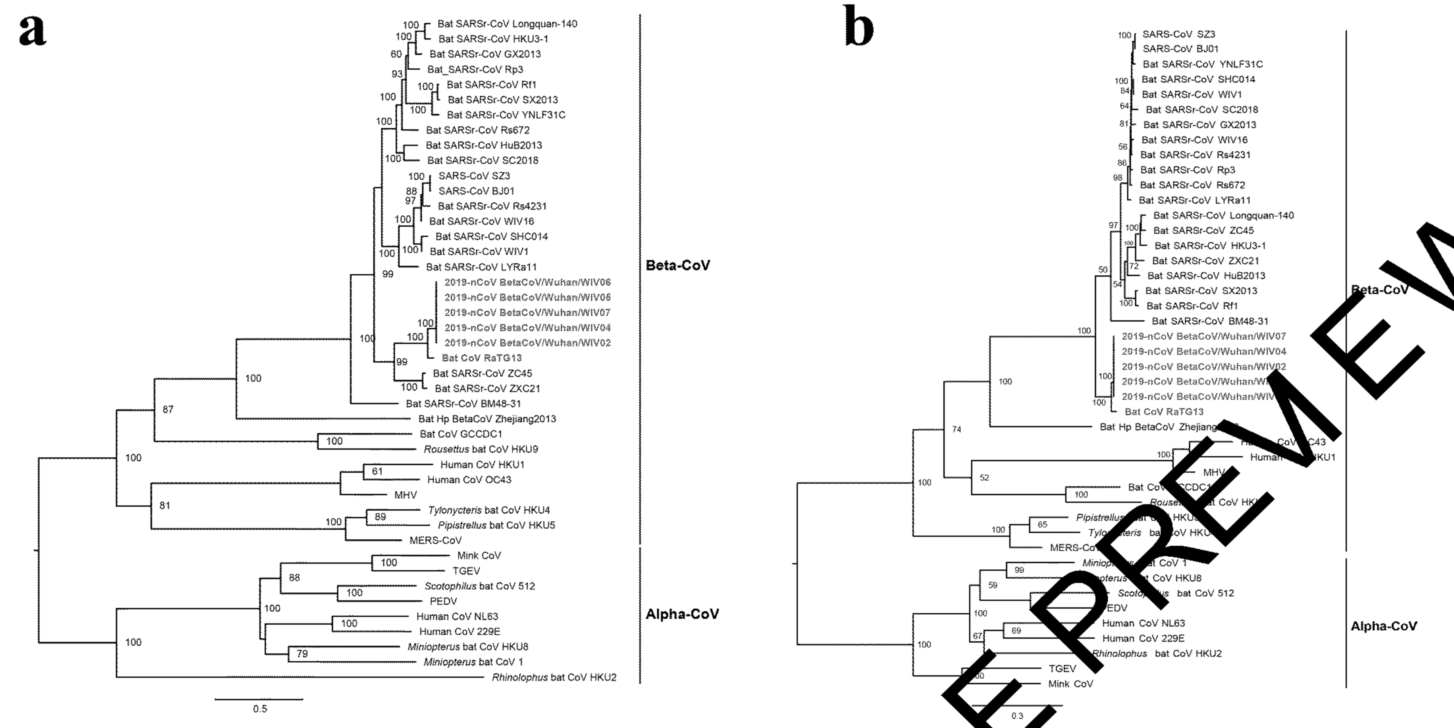

Extended Data Fig. 2 | Phylogenetic tree base on the complete S (a) and RdRp (b) gene sequences of coronaviruses. 2019-nCoV and bat CoV RaTG13 are shown in bold and in red. The trees were constructed by the maximum likelihood method using the GTR+G substitution model with bootstrap values determined by 1000 replicates. Bootstraps > 50% are shown.

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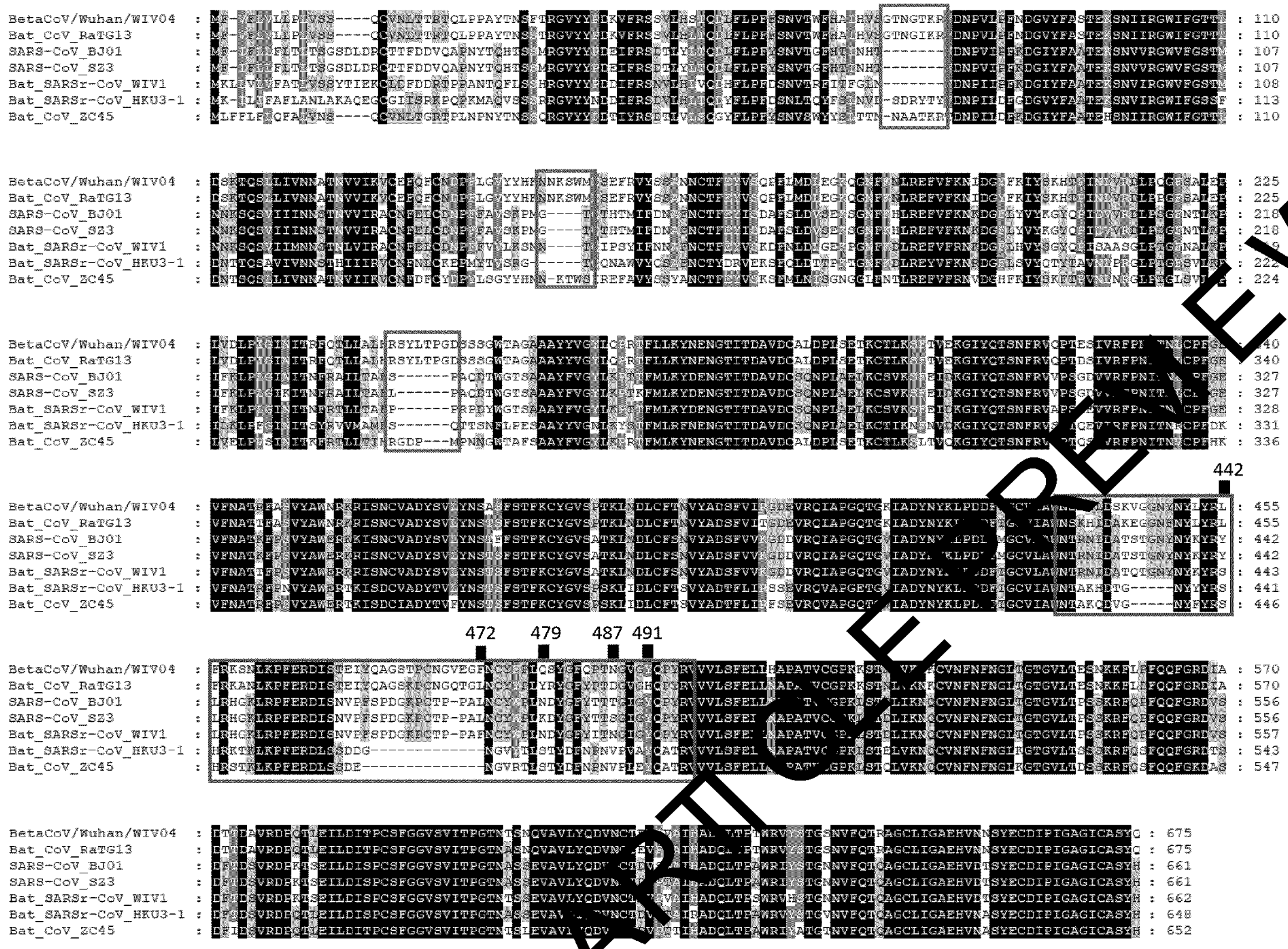

Extended Data Fig. 3 | Amino acid sequence alignment of the S1 protein of the 2019-nCoV with SARS-CoV and selected bat SARSr-CoVs. The receptor-binding motif of SARS-CoV and the homologous region of other coronaviruses are indicated by the red box. The key amino acid residues involved in the interaction with human ACE2 are numbered on top of the aligned sequences. The short insertions in the N-terminal domain of the novel coronavirus are indicated by the blue boxes. Bat CoV RaTG13 was identified from *R. affinis* in Yunnan Province. Bat CoV ZC45 was identified from *R. sinicus* in Zhejiang Province.

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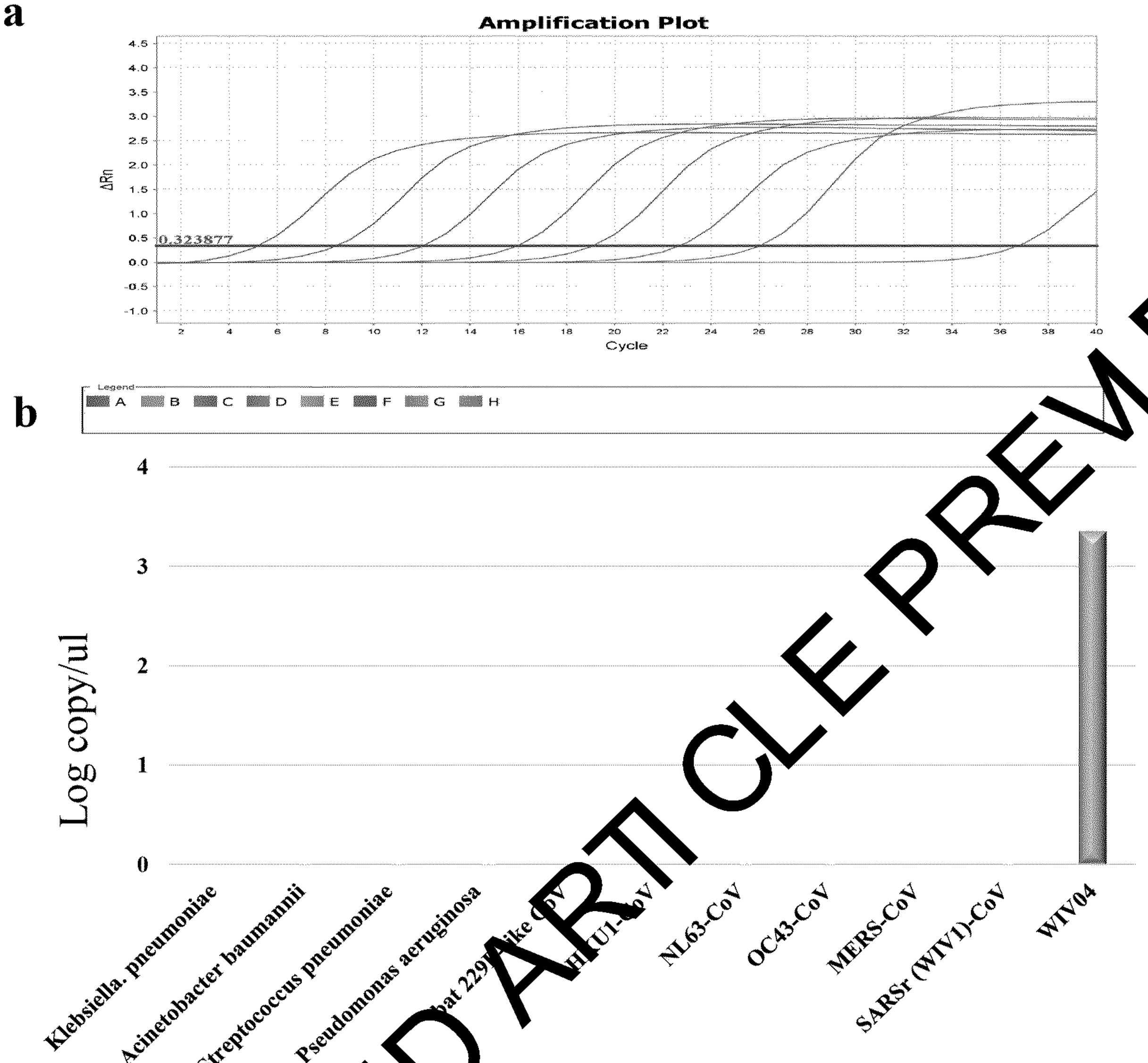

Extended Data Fig. 4 | Molecular detection method set up for 2019-nCoV. a, standard curve for qPCR primers. PCR product of spike gene that was serial diluted to 10^8 to 10^1 (from left to right) was used as template. Primer sequence and experiment condition can be found in material and methods. **b**, specificity of qPCR primers. Nucleotide samples from the indicated pathogens were used.

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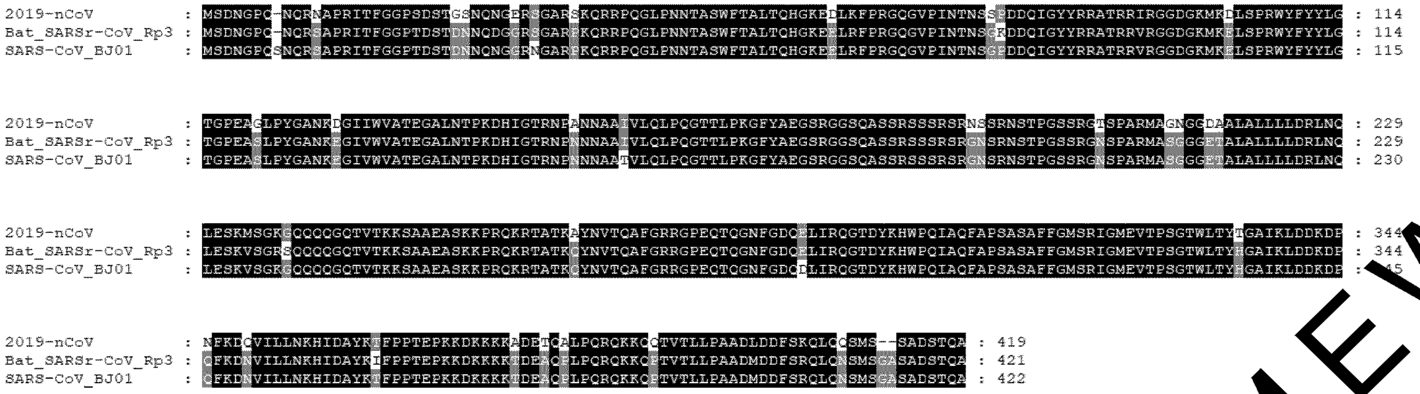

Extended Data Fig. 5 | Amino acid sequence alignment of the nucleocapsid protein of 2019-nCoV with bat SARSr-CoV Rp3 and SARS-CoV BJ01.

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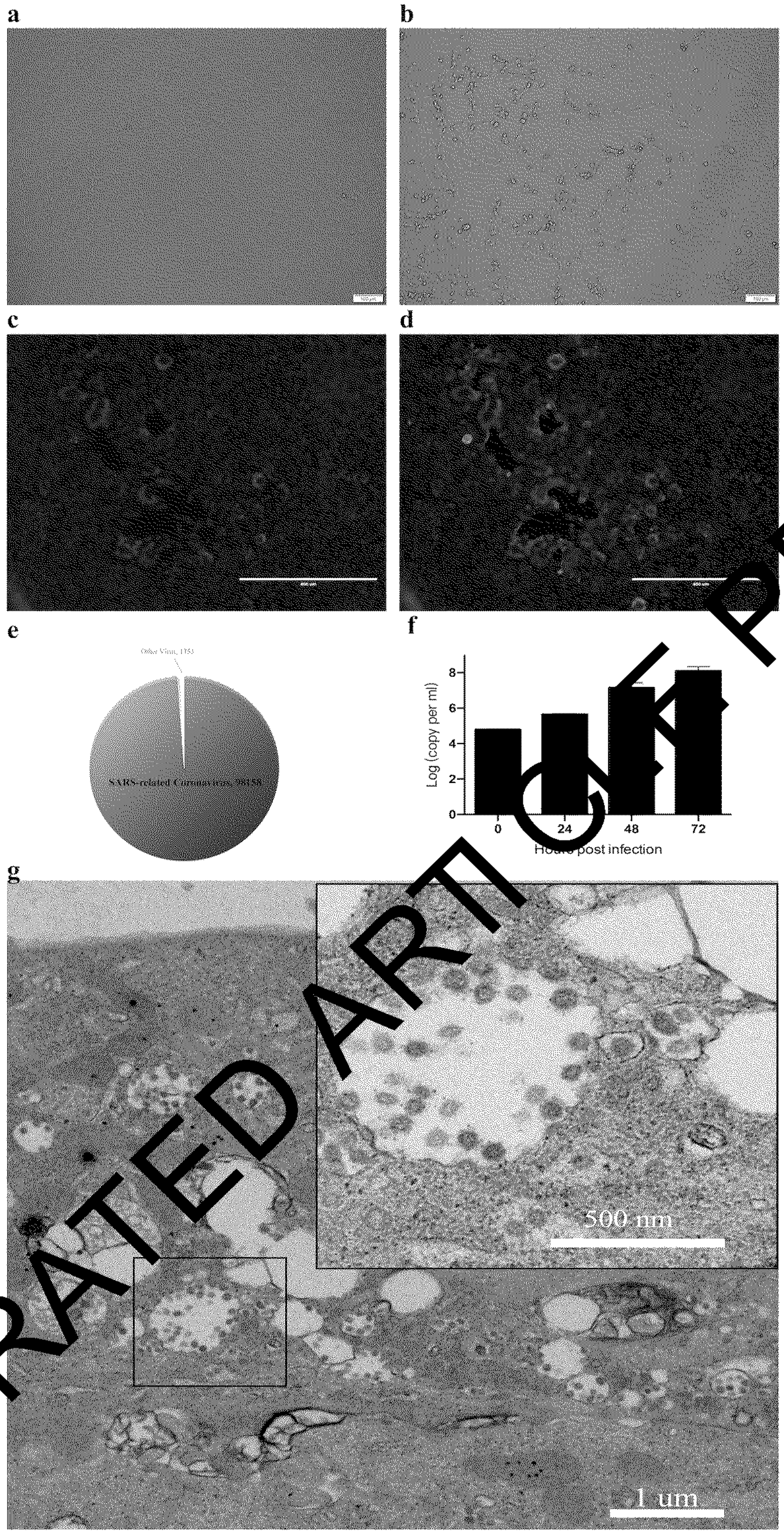

Extended Data Fig. 6 | Isolation and antigenic characterization of 2019-nCoV. Vero E6 cells are shown at 24 hours post infection with mock (**a**) or 2019-nCoV (**b**). (**c**) and (**d**) are mock or 2019-nCoV infected samples stained with rabbit serum raised against recombinant SARSr-CoV Rp3 N protein (red) and DAPI (blue). The experiment was conducted two times independently with similar results. **e** and **f**, pie charts illustrating ratio of reads number related to 2019-nCoV among total viral related reads in metagenomics analysis of Vero (**e**) and Huh7 (**f**) cell culture supernatant. (**g**) viral particles in the ultrathin sections under electron microscope at 200 kV, sample from viral infected Vero E6 cells.

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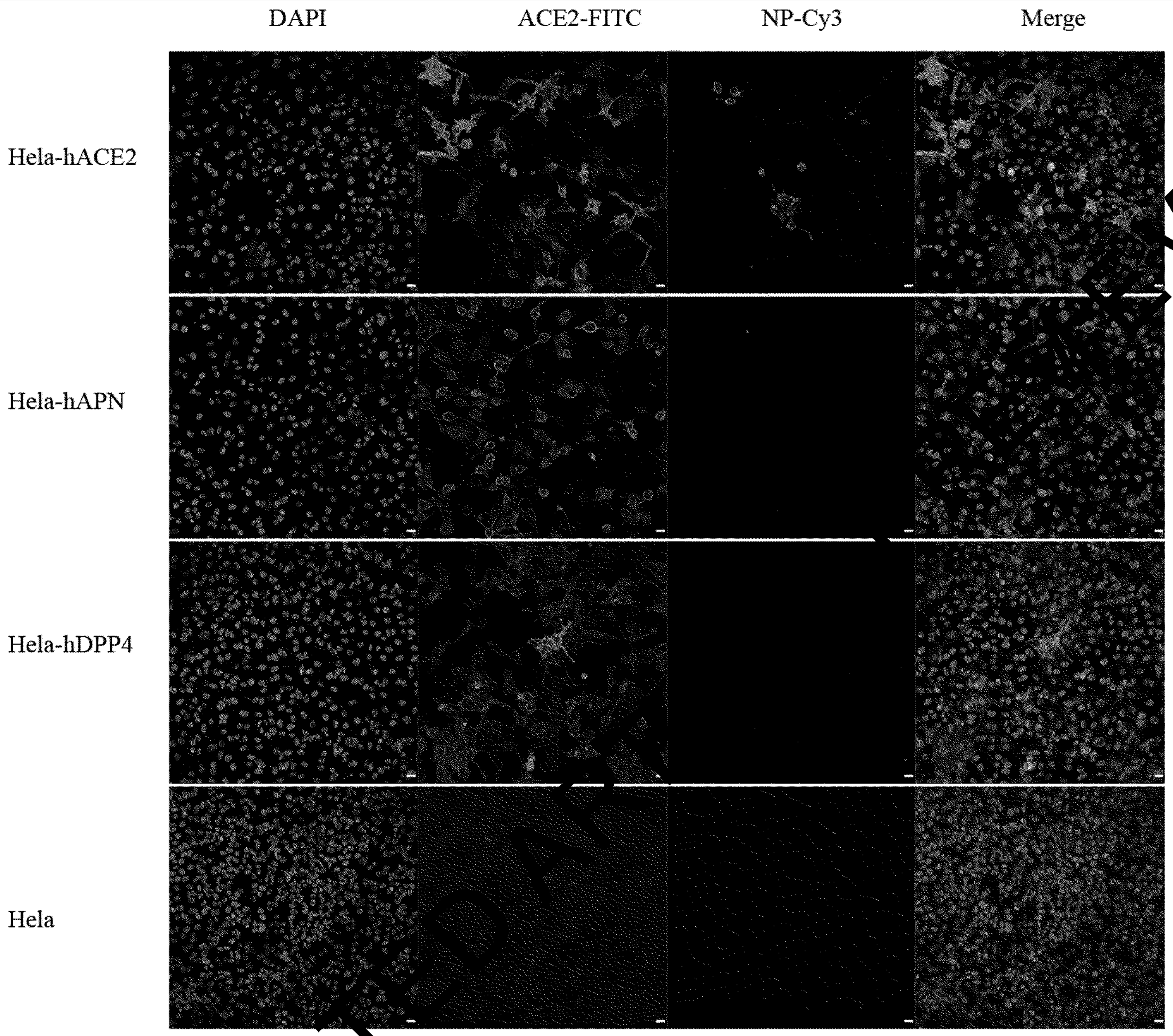

Extended Data Fig. 7 | Analysis of 2019-nCoV receptor usage. Determination of virus infectivity in HeLa cells with or without the expression of human APN and DPP4. ACE2 protein (green), viral protein (red) and nuclei (blue) were shown. Scale bar=10 um.

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Extended Data Table 1 | Patient information and their diagnosis history (some records are missing)

Patient No.	Gender	Age	Date of Onset	Date of Admission	Symptoms When Admitted	Current Status (2020.01.13)	Diagnosis history
ICU-01*	Male	62	2019.12.12	2019.12.27	fever	recover, discharged	negative
ICU-04	Male	32	2019.12.19	2019.12.29	fever, cough, dyspnea	fever, intermittent cough	negative
ICU-05	Male	40	2019.12.17	2019.12.27	fever (38 °C), expectoration, malaise, dyspnea	fever, malaise, intermittent cough	AdV (IgM)
ICU-06	Female	49	2019.12.23	2019.12.27	fever (37.9 °C), palpitation	fever, malaise, cough	Coronavirus (nt)
ICU-08	Female	52	2019.12.22	2019.12.29	fever (38.5 °C), expectoration, malaise, dyspnea	recover, discharged	Streptococcus pneumoniae (nt)
ICU-09	Male	40	2019.12.22	2019.12.28	fever (38.5 °C), expectoration	fever (38.5 °C), malaise, expectoration, dizziness	negative
ICU-10	Male	56	2019.12.20	2019.12.20	fever, dyspnea, chest tightness	fever, malaise, cough, dyspnea	negative

All patients are seafood market sellers or deliverymen except ICU-01, whose contact history is unclear. All patients were in intensive care unit (ICU) during the first investigation, and now in stable condition. Blood IgM tests have been performed for the following respiratory pathogens for all patients: legionella pneumophilia, mycoplasma pneumoniae, chlamydia pneumoniae, respiratory syncytial virus, adenovirus, rickettsia, influenza A virus, influenza B virus, parainfluenza virus. *This patient reported fever on 2019.12.12, and then recovered without medical treatment. He came back to hospital on 2019.12.27 due to fever. His wife was also sick and admitted to hospital. Both of them were recovered.

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Extended Data Table 2 | Laboratory detection results

		First sampling-2019.12.30			Second sampling-2020.01.10			
Patient No.	Test No.	BALF	Oral Swab	Blood (Ab)	Oral Swab	Anal Swab	Blood (PCR)	Blood (Ab)
ICU-01	WIV01	-	Ct=32.0	NA	NA	NA	NA	NA
ICU-04	WIV02[#]	Ct=17.6	Ct=26.6	NA	-	-	-	+
ICU-05	WIV03	Ct=27.0	Ct=31.9	NA	-	-	-	+
ICU-06	WIV04[#*]	Ct=18.3	Ct=27.7	+	-	-	-	+
ICU-08	WIV05[#]	Ct=24.1	-	NA	NA	NA	NA	NA
ICU-09	WIV06[#]	Ct=21.6	Ct=29.4	NA	-	-	-	+
ICU-10	WIV07[#]	Ct=25.7	Ct=24.0	NA	-	-	-	+

Samples from two patients (ICU-01 and ICU-08) were not available during the second investigation. They have been discharged from hospital. We did serial test for ICU-06 patient at the following date: 19.12.30, 19.12.31, 20.01.01 and 20.01.10, corresponding to seven, eight, nine and eighteen days upon disease onset (19.12.23). Table shows molecular and serological (IgM and IgG) detection results for 2019-nCoV. [$]Full-length genome obtained. *Virus isolated.

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Extended Data Table 3 | Genomic comparison of 2019-nCoV WIV04 with SARS-CoVs and bat SARSr-CoVs

	Sequence identities with SARS-CoVs & bat SARSr-CoVs (nt/aa %)											
	Full-length genome	ORF1a	ORF1b	S	ORF3a	E	M	ORF6	ORF7a	ORF7b	ORF8	N
SARS-CoV GZ02	79.6	76.0/80.9	86.2/95.7	73.4/77.0	75.6/73.4	94.7/96.0	85.4/90.5	76.3/68.9	82.8/86.0	84.8/81.4	52.0/31.6	87.7/91.2
SARS-CoV BJ01	79.6	76.0/80.8	86.2/95.7	73.4/76.9	75.3/72.6	94.7/96.0	85.6/90.5	75.8/67.2	82.8/86.0	84.8/81.4	51.1/-	88.8/91.2
SARS-CoV Tor2	79.6	76.0/80.9	86.2/95.8	73.4/76.7	75.4/72.6	94.7/96.0	85.6/90.5	76.3/68.9	82.8/86.0	84.8/81.4	51.1/-	88.8/91.2
SARS-CoV SZ3	79.6	76.0/81.0	86.2/95.8	73.4/76.9	75.4/72.6	94.7/96.0	85.3/90.0	76.3/68.9	82.8/86.0	84.8/81.4	52.3/31.6	[illegible]
SARS-CoV PC4-227	79.5	76.0/80.8	86.1/95.6	73.4/76.7	75.5/72.6	94.7/96.0	85.1/90.0	75.8/68.9	82.8/86.0	84.8/81.4	52.3/-	[illegible]
Bat SARr-CoV RaTG13	96.2	96.0/98.0	97.3/99.3	93.1/97.7	96.3/97.8	99.6/100	95.5/99.6	98.4/100	95.6/97.5	99.2/97.7	97.0/95.0	[illegible]
Bat SARr-CoV WIV1	79.7	76.0/80.7	85.9/95.8	73.4/77.6	76.1/74.5	95.6/96.0	84.8/90.0	78.0/73.8	85.0/88.4	85.6/83.7	[illegible]	88.5/90.9
Bat SARSr-CoV WIV16	79.7	75.9/81.0	86.1/95.6	73.1/77.8	76.1/74.5	95.6/96.0	84.8/90.0	77.4/72.1	85.0/88.4	85.6/83.7	[illegible]	[illegible]
Bat SARSr-CoV SHC014	79.6	75.9/80.9	85.9/95.8	73.3/77.7	76.1/74.5	95.6/96.0	84.8/90.0	78.0/70.5	84.4/88.4	[illegible]	65.8/58.7	88.6/90.9
Bat SARSr-CoV Rs4231	79.7	76.0/81.0	86.2/95.8	72.9/77.5	75.8/74.1	94.3/94.7	84.4/90.0	76.9/67.2	85.0/88.4	[illegible]	[illegible]	88.8/91.4
Bat SARSr-CoV YNLF31C	79.0	75.7/80.6	85.8/95.7	71.4/75.5	75.0/71.2	94.3/96.0	84.7/89.6	76.9/70.5	83.1/87.6	[illegible]	[illegible]	88.3/90.5
Bat SARSr-CoV LYRa11	79.6	75.8/80.6	85.7/95.6	73.9/77.3	77.2/76.3	94.7/94.7	85.1/90.0	78.5/70.5	82.0/85.1	[illegible]	66.7/57.9	89.0/91.6
Bat SARSr-CoV ZC45	88.1	91.0/95.7	86.1/96.0	77.8/82.3	87.8/90.9	98.7/100	93.4/98.6	95.2/93.4	[illegible]	[illegible]	88.5/94.2	91.1/94.3
Bat SARSr-CoV ZXC21	88.0	90.9/95.7	86.2/95.8	77.1/81.7	88.9/92.0	98.7/100	93.4/98.6	95.2/93.4	[illegible]	95.5/93.0	88.5/94.2	91.2/94.3
Bat SARSr-CoV HuB2013	79.6	76.3/81.2	85.3/95.7	73.1/76.8	75.4/75.5	95.2/94.7	85.3/91.0	[illegible]	[illegible]	85.6/83.7	62.0/49.6	88.9/91.6
Bat SARSr-CoV GX2013	79.1	75.9/80.8	86.0/95.9	73.1/77.1	75.6/73.0	94.7/96.0	84.8/91.4	[illegible]	85.0/86.8	84.1/79.1	51.4/31.6	87.9/90.2
Bat SARSr-CoV SX2013	78.9	76.2/80.6	85.1/95.5	71.2/75.5	74.7/71.2	94.3/93.3	83.0/89.6	[illegible]	84.2/86.8	85.6/83.7	49.7/30.4	86.9/90.2
Bat SARSr-CoV SC2018	79.4	75.8/80.7	85.5/95.2	72.7/76.4	75.0/71.2	94.3/96.0	[illegible]	80.0/71.8	85.2/87.6	84.8/83.7	66.1/55.4	88.2/91.2
Bat SARSr-CoV Rs672	79.6	76.0/80.9	85.9/95.8	72.8/76.2	75.2/71.9	95.2/96.0	84.8/89.6	[illegible]	84.7/88.4	85.6/83.7	65.8/58.7	87.9/91.2
Bat SARSr-CoV Rp3	79.5	75.9/80.5	86.0/95.7	73.1/77.2	74.9/74.8	95.2/96.0	[illegible]	76.9/68.9	83.9/89.3	84.8/83.7	66.4/56.2	88.4/90.7
Bat SARSr-CoV Rf1	78.8	76.2/80.6	84.8/95.3	71.1/75.7	74.3/69.0	[illegible]	83.3/89.6	79.0/68.9	84.2/86.8	84.1/83.7	50.6/31.3	86.8/89.5
Bat SARSr-CoV HKU3-1	79.4	76.1/80.9	84.9/95.1	73.4/77.9	75.8/73.4	[illegible]	84.7/91.0	75.3/67.2	85.0/89.3	84.1/79.1	66.4/57.0	88.3/90.0

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Extended Data Table 4 | Virus neutralization test (VNT) of serum samples

Samples	VNT titre for nCoV-2019
Healthy people #1 from Wuhan	neg
Healthy people #2 from Wuhan	neg
Horse anti-SARS-CoV serum	>1:80
WIV02	>1:80
WIV03	1:40
WIV04	>1:80
WIV06	>1:80
WIV07	>1:80

Each serum sample was tested in triplicate. Two healthy people from Wuhan, five patient serum samples and a horse anti-SARS-CoV anti-serum were used. 120 $TCID_{50}$ viruses were used each well. Serum samples were used in a dilution from 1:10, 1:20, 1:40 to 1:80.

ACCELERATED ARTICLE PREVIEW

nature research

Corresponding author(s): Zheng-Li Shi

Last updated by author(s): Jan 26, 2020

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used.
Data analysis	BWA (v0.712-r1039), Cutadapt (v1.18), Geneious (v11.0.3), MEGAHIT (v1.2.9), Clone Manager Professional Suite 8, MAFFT (v7.307), MGmapper (PE2.24 and SE2.24), PAL2NAL (version 14), Clustal Omega (version 1.2.4), RAxML (version 0.9.0)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Sequence data that support the findings of this study have been deposited in GISAID with the accession no. EPI_ISL_402124 and EPI_ISL_402127-402130.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Samples of seven pneumonia patients are available from the clinical hospital to be sent to Wuhan Institute of Virology for pathogen identification. The coronavirus genome sequences were obtained from 5 different patients and shared >99.9% identity, suggesting they were infected by the same virus. Therefore, the sample size is sufficient for conducting the following study which aims to identify and characterize the causative agent of this pneumonia outbreak.
Data exclusions	No data excluded
Replication	The authors guarantee the findings are reliably reproducible. At least three independent experiments were performed, which was stated in the text.
Randomization	Samples were chosen randomly.
Blinding	We were blinded when choosing samples.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study	
☐	☒	Antibodies
☐	☒	Eukaryotic cell lines
☒	☐	Palaeontology
☒	☐	Animals and other organisms
☐	☒	Human research participants
☒	☐	Clinical data

Methods

n/a	Involved in the study	
☒	☐	ChIP-seq
☒	☐	Flow cytometry
☒	☐	MRI-based neuroimaging

Antibodies

Antibodies used	1. SARSr-CoV Rp3 NP antibody made in house; 2. Cy3-conjugated mouse anti-rabbit IgG; 3. Anti-Human IgG-HRP conjugated monoclonal antibody (Kyab Biotech Co., Ltd, Wuhan, China, dilution: 1:40000); 4. Anti-Rp3 NP-HRP conjugated (Kyab Biotech Co., Ltd, Wuhan, China, dilution: 1:4000); 5. FITC-labelled goat anti-mouse IgG H&L (Abcam, ab96879, dlilution 1:100); 6. cyanin 3-conjugated goat anti-rabbit IgG (Abcam,ab6939, dilution: 1:50); 7. mouse anti-S tag monoclonal antibody made in house (1:10000)
Validation	The house-made SARSr-CoV Rp3 NP antibodies and anti-S tag monoclonal antibody were validated in a WB. The cy3-conjugated anti-rabbit IgGs were validated in IFA. The FITC-labelled goat anti-mouse IgG H&L was validated in IHC.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	1. African green monkey origin, Vero and Vero E6 cells; 2. Human lung cell Huh7 ; 3. Human HeLa cells. All cell lines were from ATCC.
Authentication	All monkey and human cells were from ATCC with authentication. The authentication was performed by microscope morphology check, growth curve analysis or identity verification with STR analysis (for human cell lines).
Mycoplasma contamination	We confirm that all cells were tested as mycoplasma negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Participants were all 2019-nCoV infected patients.
Recruitment	Samples were sent to Wuhan Institute of Virology by hospital for pathogen identification.
Ethics oversight	Wuhan Jinyintan Hospital (the co-authored institution)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

To: Baric, Ralph S[rbaric@email.unc.edu]
Cc: Shore, Carolyn[CShore@nas.edu]; Peter Daszak[daszak@ecohealthalliance.org]; Kristian Andersen Trevor Bedford (trevor@bedford.io)[trevor@bedford.io]; Gigi Gronvall[ggronvall@jhu.edu]; Tom Inglesby (tinglesby@jhu.edu)[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]; Chao, Samantha[SChao@nas.edu]; Pope, Andrew[APope@nas.edu]
From: Chakravarti, Aravinda[Aravinda.Chakravarti@nyulangone.org]
Sent: Tue 2/4/2020 1:15:28 PM (UTC-05:00)
Subject: Re: URGENT: Please review by NOON if at all possible...

Sorry in faculty recruitment today…I am happy with the letter particularly given the corrections/changes suggested by the experts in this area. I think saying not engineered is stronger than the CURRENT data are consistent with natural evolution is better. The call for more data from earlier times is important as is a clear statement that the data and analyses be shared openly (the Academy can endorse the Wellcome Trust statement) so that a scientific consensus can emerge. Its perhaps important to add that many scientific and medical questions remain to be answered which is why additional data are needed.

On Feb 4, 2020, at 12:51 PM, Baric, Ralph S <rbaric@email.unc.edu> wrote:

[EXTERNAL]

This is the right paper. Ralph

From: Shore, Carolyn <CShore@nas.edu>
Sent: Tuesday, February 4, 2020 12:43 PM
To: Peter Daszak <daszak@ecohealthalliance.org>; 'Chakravarti, Aravinda' <Aravinda.Chakravarti@nyulangone.org>; Kristian Andersen ·; Baric, Ralph S <rbaric@email.unc.edu>; Trevor Bedford (trevor@bedford.io) <trevor@bedford.io>; Gigi Gronvall <ggronvall@jhu.edu>; Tom Inglesby (tinglesby@jhu.edu) <tinglesby@jhu.edu>; Stanley Perlman (stanley-perlman@uiowa.edu) <stanley-perlman@uiowa.edu>
Cc: Chao, Samantha <SChao@nas.edu>; Pope, Andrew <APope@nas.edu>
Subject: RE: URGENT: Please review by NOON if at all possible...

Thank you, all, for your input on the draft letter. A couple of clarifying questions regarding citations:

- Ralph – is the attached article the appropriate citation for your comment regarding the closest relative of 2019-nCoV or is there another citation we should reference?
- Are there any other articles that we should cite that examine the origin of 2019-nCoV specifically?

Best,
Carolyn

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, February 4, 2020 12:01 PM
To: Pope, Andrew <APope@nas.edu>; 'Chakravarti, Aravinda' <Aravinda.Chakravarti@nyulangone.org>; Kristian Andersen ·; Ralph Baric (rbaric@email.unc.edu) <rbaric@email.unc.edu>; Trevor Bedford (trevor@bedford.io) <trevor@bedford.io>; Gigi Gronvall <ggronvall@jhu.edu>; Tom Inglesby (tinglesby@jhu.edu) <tinglesby@jhu.edu>; Stanley Perlman (stanley-perlman@uiowa.edu) <stanley-perlman@uiowa.edu>
Cc: Shore, Carolyn <CShore@nas.edu>; Chao, Samantha <SChao@nas.edu>
Subject: RE: URGENT: Please review by NOON if at all possible...
Importance: High

I agree with all of the other comments so far sent in, and want to add the following:

1) In the 3rd paragraph, it's important to add "including further samples from wildlife", and perhaps the rationale for this "to identify other viruses closely related to nCoV"
2) Re. references for #3 that there are current and planned studies underway on the bat origins of CoVs. Here are some references to pick from if they make sense:

- Latinne A, Hu B, Olival KJ, et al.; Origin and cross-species transmission of bat coronaviruses in China. *Nature Communications* 2020;**In review**.
- Wang N, Li S-Y, Yang X-L, et al.; Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China. *Virologica Sinica* 2018. doi: 10.1007/s12250-018-0012-7.
- Hu B, Zeng L-P, Yang X-L, et al.; Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens* 2017;**13**(11):e1006698. doi: 10.1371/journal.ppat.1006698.
- Zhou P, Fan H, Lan T, et al.; Fatal Swine Acute Diarrhea Syndrome caused by an HKU2-related Coronavirus of Bat Origin. *Nature* 2018

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

From: Pope, Andrew [mailto:APope@nas.edu]
Sent: Tuesday, February 4, 2020 9:11 AM
To: 'Chakravarti, Aravinda'; Kristian Andersen); Ralph Baric (rbaric@email.unc.edu); Trevor Bedford (trevor@bedford.io); Peter Daszak; Gigi Gronvall; Tom Inglesby (tinglesby@jhu.edu); Stanley Perlman (stanley-perlman@uiowa.edu)
Cc: Shore, Carolyn; Chao, Samantha
Subject: URGENT: Please review by NOON if at all possible...
Importance: High

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a “Based on Science” web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the data needs that are identified. We think it would be helpful to be a bit more specific, but don’t want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.
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E: Veronika.Worosz@nyulangone.org

To: Baric, Ralph S[rbaric@email.unc.edu]; Saif, Linda[saif.2@osu.edu]; JMHUGHE@emory.edu[jmhughe@emory.edu]; Rita Colwell[rita.colwell@cosmosid.com]; rcolwell@umiacs.umd.edu[rcolwell@umiacs.umd.edu]; rcolwell@umd.edu[rcolwell@umd.edu]; Wang Linfa[linfa.wang@duke-nus.edu.sg]; Hume Field[hume.field@ecohealthalliance.org]
Cc: Alison Andre[andre@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Hongying Li[li@ecohealthalliance.org]; William B. Karesh[karesh@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]
From: Peter Daszak[daszak@ecohealthalliance.org]
Sent: Thur 2/6/2020 12:43:40 AM (UTC-05:00)
Subject: A Statement in support of the scientists, public health and medical professionals of China
Statement of support, 2019nCoV China Final.docx

Dear Ralph, Linda, Jim, Rita, Linfa and Hume,

I've been following the events around the novel coronavirus emergence in China very closely and have been dismayed by the recent spreading of rumors, misinformation and conspiracy theories on its origins. These are now specifically targeting scientists with whom we've collaborated for many years, and who have been working heroically to fight this outbreak and share data with unprecedented speed, openness and transparency. These conspiracy theories threaten to undermine the very global collaborations that we need to deal with a disease that has already spread across continents.

We have drafted a simple statement of solidarity and support for scientists, public health and medical professionals of China, and would like to invite you to join us as the first signatories. If you agree, we will send this letter to a group of around half-a-dozen other leaders in the field and then disseminate this widely with a sign-up webpage for others to show their support by signing up to its language. I will then personally present this at my plenary during the ICID 2020 conference in Malaysia in two weeks, with the goal of also getting widespread attention in SE Asia to our support for the work that our colleagues in China are undertaking.

I sincerely hope you can join us. Please review the letter, and let me know if you are willing to join Billy Karesh and myself as co-signatories. Also, please confirm your title and affiliation that will be shown in the letter. We plan to make circulate this widely to coincide with a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, which will likely be released tomorrow or Friday.

Thank you for your consideration and support of the scientific and public health community around the world!

Cheers,

Peter

Peter Daszak
President

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460 West 34th Street – 17th Floor
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Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

Statement in Support of the Scientists, Public Health, and Medical Professionals of China Combating the Novel Coronavirus Outbreak

We, the undersigned, are scientists who have followed the emergence of 2019-nCoV, and are deeply concerned about its global impact on people's health and well-being. We have watched as the scientists, public health and medical professionals of China have worked heroically to rapidly identify the pathogen behind this outbreak, put in place significant measures to reduce its impact, and share their results transparently with the global health community. We sign this statement in solidarity with all scientists, public health, and medical professionals in China who continue to save lives and protect *global* health during the challenge of this novel coronavirus outbreak. We want you to know that we are all in this together, with you in front of us on the battlefield against the novel coronavirus.

The rapid, open and transparent sharing of data on 2019-nCoV is now being threatened by rumors and misinformation around the origins of this outbreak. We stand together to strongly condemn conspiracy theories suggesting that 2019-nCoV does not have a natural origin. Scientific evidence overwhelmingly suggests that this virus originated in wildlife, as have so many other emerging diseases (*1-4*). This is further supported by a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, and by the scientific communities they represent (INSERT REF). Conspiracy theories will do nothing but create fear, rumors, and prejudice that jeopardize our global collaboration in the fight against this virus. We need to prioritize scientific evidence and unity over misinformation and conjecture now. We want you all to know that **we stand with you**, the science and health professionals of China, in your fight against this virus.

We invite others to join us in supporting the scientists, public health, and medical professionals of Wuhan and across China. Stand with our colleagues on the front-line!

Please add your name in an act of support by going to [INSERT LINK HERE].

Signatories

Dr. Peter Daszak, President, EcoHealth Alliance
Dr. Jim Hughes, Professor Emeritus, Emory University
Dr. Rita Colwell, former Director of National Science Foundation
Dr. Ralph Baric, Professor, The University of North Carolina, Chapel Hill
Dr. Linda Saif, Distinguished University Professor, The Ohio State University
Dr. Billy Karesh, Executive Vice President, EcoHealth Alliance
Dr. Linfa Wang, Professor, Duke-NUS Medical School
Dr. Hume Field, Honorary Professor, The University of Queensland

References

1. P. Zhou *et al.*, A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, (2020).
2. R. Lu *et al.*, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, (2020).
3. N. Zhu *et al.*, A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, (2020).
4. L. Ren *et al.*, Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chin Med J. Epub ahead of print*, (2020).

To: Peter Daszak[daszak@ecohealthalliance.org]; Baric, Ralph S[rbaric@email.unc.edu]; Saif, Linda[saif.2@osu.edu]; jmhughe@emory.edu[jmhughe@emory.edu]; Rita Colwell[rita.colwell@cosmosid.com]; rcolwell@umiacs.umd.edu[rcolwell@umiacs.umd.edu]; rcolwell@umd.edu[rcolwell@umd.edu]; Wang Linfa[linfa.wang@duke-nus.edu.sg]
Cc: Alison Andre[andre@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Hongying Li[li@ecohealthalliance.org]; William B. Karesh[karesh@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]
From: Hume Field[hume.field@ecohealthalliance.org]
Sent: Thur 2/6/2020 4:10:50 AM (UTC-05:00)
Subject: RE: A Statement in support of the scientists, public health and medical professionals of China
Statement of support 2019nCoV China Final_HF.docx

Peter, some suggested edits to the statement for consideration, with the benefit of time..

Hume

From: Hume Field <hume.field@ecohealthalliance.org>
Sent: Thursday, 6 February 2020 4:35 PM
To: 'Peter Daszak' <daszak@ecohealthalliance.org>; 'Ralph Baric (rbaric@email.unc.edu)' <rbaric@email.unc.edu>; 'Saif, Linda' <saif.2@osu.edu>; 'jmhughe@emory.edu' <jmhughe@emory.edu>; 'Rita Colwell' <rita.colwell@cosmosid.com>; 'rcolwell@umiacs.umd.edu' <rcolwell@umiacs.umd.edu>; 'rcolwell@umd.edu' <rcolwell@umd.edu>; 'Wang Linfa' <linfa.wang@duke-nus.edu.sg>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>; Hongying Li <li@ecohealthalliance.org>; William B. Karesh <karesh@ecohealthalliance.org>; Robert Kessler <kessler@ecohealthalliance.org>
Subject: RE: A Statement in support of the scientists, public health and medical professionals of China

Count me in Peter. I had thought/hoped that this conspiracy stuff would fade, but clearly not. So yes, I agree it's time to actively counter it, and express peer support for the world class Chinese scientists doing such great work, yet being publicly and professionally impugned.

Well done mate.
Hume

Hume Field BVSc MSc PhD MACVS
Honorary Professor | **University of Queensland** | Australia
Science & Policy Advisor **| EcoHealth Alliance** | USA
Director | **Jeppesen Field Consulting** | Australia.

Ph:

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Thursday, 6 February 2020 3:44 PM
To: Ralph Baric (rbaric@email.unc.edu) <rbaric@email.unc.edu>; Saif, Linda <saif.2@osu.edu>; jmhughe@emory.edu; Rita Colwell <rita.colwell@cosmosid.com>; rcolwell@umiacs.umd.edu; rcolwell@umd.edu; Wang Linfa <linfa.wang@duke-nus.edu.sg>; Hume Field <hume.field@ecohealthalliance.org>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>; Hongying Li <li@ecohealthalliance.org>; William B. Karesh <karesh@ecohealthalliance.org>; Robert Kessler <kessler@ecohealthalliance.org>
Subject: A Statement in support of the scientists, public health and medical professionals of China
Importance: High

Dear Ralph, Linda, Jim, Rita, Linfa and Hume,

I've been following the events around the novel coronavirus emergence in China very closely and have been dismayed by the recent spreading of rumors, misinformation and conspiracy theories on its origins. These are now specifically targeting scientists with whom we've collaborated for many years, and who have been working heroically to fight this outbreak and share data with unprecedented speed, openness and transparency. These conspiracy theories threaten to undermine the very global collaborations

that we need to deal with a disease that has already spread across continents.

We have drafted a simple statement of solidarity and support for scientists, public health and medical professionals of China, and would like to invite you to join us as the first signatories. If you agree, we will send this letter to a group of around half-a-dozen other leaders in the field and then disseminate this widely with a sign-up webpage for others to show their support by signing up to its language. I will then personally present this at my plenary during the ICID 2020 conference in Malaysia in two weeks, with the goal of also getting widespread attention in SE Asia to our support for the work that our colleagues in China are undertaking.

I sincerely hope you can join us. Please review the letter, and let me know if you are willing to join Billy Karesh and myself as co-signatories. Also, please confirm your title and affiliation that will be shown in the letter. We plan to make circulate this widely to coincide with a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, which will likely be released tomorrow or Friday.

Thank you for your consideration and support of the scientific and public health community around the world!

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Tel.
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

Statement in Support of the Scientists, Public Health, and Medical Professionals of China Combating the Novel Coronavirus Outbreak

We, the undersigned, are emerging infectious disease scientists who have closely followed the emergence of 2019-nCoV, and are deeply concerned about its current and potential global impact on human health and well-being. We have watched as the scientists, public health and medical professionals of China have worked diligently and effectively to rapidly identify the pathogen behind this outbreak, put in place significant measures to reduce its impact, and share their results transparently with the global health community. This effort, notwithstanding the benefit of hindsight, has been remarkable.

We sign this statement in solidarity with all scientists, public health, and medical professionals in China who continue to save lives and protect *global* human health during the challenge of this novel coronavirus outbreak. We are all in this together, with our Chinese counterparts in the fore, against this new virus threat.

The rapid, open and transparent sharing of data on 2019-nCoV is now being threatened by rumors and misinformation around the origins of this outbreak. We stand together to strongly condemn conspiracy theories suggesting that 2019-nCoV does not have a natural origin. Scientific evidence overwhelmingly suggests that this virus originated in wildlife, as have so many other emerging diseases (*1-4*). This is further supported by a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, and by the scientific communities they represent (INSERT REF). Conspiracy theories do nothing but create fear, rumors, and prejudice that jeopardize our global collaboration in the fight against this virus. We need to promote scientific evidence and unity over misinformation and conjecture now. We want you, the science and health professionals of China, to know that **we stand with you** in your fight against this virus.

We invite others to join us in supporting the scientists, public health, and medical professionals of Wuhan and across China. Stand with our colleagues on the front-line!

Please add your name in an act of support by going to [INSERT LINK HERE].

Signatories

Dr. Peter Daszak, President, EcoHealth Alliance
Dr. Jim Hughes, Professor Emeritus, Emory University
Dr. Rita Colwell, former Director of National Science Foundation
Dr. Ralph Baric, Professor, The University of North Carolina, Chapel Hill
Dr. Linda Saif, Distinguished University Professor, The Ohio State University
Dr. Billy Karesh, Executive Vice President, EcoHealth Alliance
Dr. Linfa Wang, Professor, Duke-NUS Medical School
Dr. Hume Field, Honorary Professor, School of Veterinary Science, The University of Queensland

References

1. P. Zhou *et al.*, A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, (2020).
2. R. Lu *et al.*, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, (2020).
3. N. Zhu *et al.*, A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, (2020).
4. L. Ren *et al.*, Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chin Med J. Epub ahead of print*, (2020).

To: Hume Field[hume.field@ecohealthalliance.org]
Cc: Peter Daszak[daszak@ecohealthalliance.org]; Baric, Ralph S[rbaric@email.unc.edu]; jmhughe@emory.edu[jmhughe@emory.edu]; Rita Colwell[rita.colwell@cosmosid.com]; rcolwell@umiacs.umd.edu[rcolwell@umiacs.umd.edu]; rcolwell@umd.edu[rcolwell@umd.edu]; Wang Linfa[linfa.wang@duke-nus.edu.sg]; Alison Andre[andre@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]; Hongying Li[li@ecohealthalliance.org]; William B. Karesh[karesh@ecohealthalliance.org]; Robert Kessler[kessler@ecohealthalliance.org]
From: Saif, Linda[saif.2@osu.edu]
Sent: Thur 2/6/2020 11:48:58 AM (UTC-05:00)
Subject: Re: A Statement in support of the scientists, public health and medical professionals of China

Hi all
I concur with this draft!
One question is whether it would be useful to add just one or 2 statements in support of why nCoV is not a lab generated virus and is naturally occurring? Seems critical to scientifically refute such claims!
Linda

Sent from my iPhone

On Feb 6, 2020, at 4:12 AM, Hume Field <hume.field@ecohealthalliance.org> wrote:

Peter, some suggested edits to the statement for consideration, with the benefit of time..

Hume

From: Hume Field <hume.field@ecohealthalliance.org>
Sent: Thursday, 6 February 2020 4:35 PM
To: 'Peter Daszak' <daszak@ecohealthalliance.org>; 'Ralph Baric (rbaric@email.unc.edu)' <rbaric@email.unc.edu>; 'Saif, Linda' <saif.2@osu.edu>; 'jmhughe@emory.edu' <jmhughe@emory.edu>; 'Rita Colwell' <rita.colwell@cosmosid.com>; 'rcolwell@umiacs.umd.edu' <rcolwell@umiacs.umd.edu>; 'rcolwell@umd.edu' <rcolwell@umd.edu>; 'Wang Linfa' <linfa.wang@duke-nus.edu.sg>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>; Hongying Li <li@ecohealthalliance.org>; William B. Karesh <karesh@ecohealthalliance.org>; Robert Kessler <kessler@ecohealthalliance.org>
Subject: RE: A Statement in support of the scientists, public health and medical professionals of China

Count me in Peter. I had thought/hoped that this conspiracy stuff would fade, but clearly not. So yes, I agree it's time to actively counter it, and express peer support for the world class Chinese scientists doing such great work, yet being publicly and professionally impugned.

Well done mate.
Hume

Hume Field BVSc MSc PhD MACVS
Honorary Professor | **University of Queensland** | Australia
Science & Policy Advisor **| EcoHealth Alliance** | USA
Director | **Jeppesen Field Consulting** | Australia.

Ph:

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Thursday, 6 February 2020 3:44 PM
To: Ralph Baric (rbaric@email.unc.edu) <rbaric@email.unc.edu>; Saif, Linda <saif.2@osu.edu>;

jmhughe@emory.edu; Rita Colwell <rita.colwell@cosmosid.com>; rcolwell@umiacs.umd.edu; rcolwell@umd.edu; Wang Linfa <linfa.wang@duke-nus.edu.sg>; Hume Field <hume.field@ecohealthalliance.org>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>; Hongying Li <li@ecohealthalliance.org>; William B. Karesh <karesh@ecohealthalliance.org>; Robert Kessler <kessler@ecohealthalliance.org>
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Thank you for your consideration and support of the scientific and public health community around the world!

Cheers,

Peter

Peter Daszak
President

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Twitter: @PeterDaszak

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<Statement of support 2019nCoV China Final_HF.docx>

To: Peter Daszak[daszak@ecohealthalliance.org]; Baric, Toni C[antoinette_baric@med.unc.edu]
Cc: Alison Andre[andre@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]
From: Baric, Ralph S[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB0D9CC80C184735A4E862C3BDD8A15D-RALPH S BAR]
Sent: Thur 2/6/2020 4:01:22 PM (UTC-05:00)
Subject: RE: No need for you to sign the "Statement" Ralph!!

I also think this is a good decision. Otherwise it looks self-serving and we lose impact. ralph

---

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Thursday, February 6, 2020 3:16 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Baric, Toni C <antoinette_baric@med.unc.edu>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>
Subject: No need for you to sign the "Statement" Ralph!!
Importance: High

I spoke with Linfa last night about the statement we sent round. He thinks, and I agree with him, that you, me and him should not sign this statement, so it has some distance from us and therefore doesn't work in a counterproductive way.

Jim Hughes, Linda Saif, Hume Field, and I believe Rita Colwell will sign it, then I'll send it round some other key people tonight. We'll then put it out in a way that doesn't link it back to our collaboration so we maximize an independent voice.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
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New York, NY 10001

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Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

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To: Chakravarti, Aravinda[Aravinda.Chakravarti@nyulangone.org]; andersen@scripps.edu[andersen@scripps.edu]; Baric, Ralph S[rbaric@email.unc.edu]; trevor@bedford.io[trevor@bedford.io]; Peter Daszak (daszak@ecohealthalliance.org)[daszak@ecohealthalliance.org]; Gigi Gronvall[ggronvall@jhu.edu]; tinglesby@jhu.edu[tinglesby@jhu.edu]; Stanley Perlman (stanley-perlman@uiowa.edu)[stanley-perlman@uiowa.edu]
Cc: Griffin Diane[dgriffi6@jhmi.edu]; Chao, Samantha[SChao@nas.edu]; Shore, Carolyn[CShore@nas.edu]; Kearney, William[WKearney@nas.edu]; Symmes, Gregory[GSymmes@nas.edu]; Behney, Clyde[CBehney@nas.edu]; Shern, Lauren[LShern@nas.edu]
From: Pope, Andrew[APope@nas.edu]
Sent: Fri 2/7/2020 8:24:57 PM (UTC-05:00)
Subject: Thanks and News about the letter

Dear all
On behalf of the National Academies I want to say thank you again for your willingness to respond so quickly to our requests for expert expert assistance in developing a rapid response to OSTP on nCoV. We couldn't have done it without you!
Please see our news posting at the following link, and let us know if you have any questions or concerns.

http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=272020&_ga=2.118407884.416011462.1581027163-581770746.1511913188

Thanks again and have a great weekend!

Andy
Sent from my "smart" phone...

To: Peter Daszak[daszak@ecohealthalliance.org]
Cc: Leo Poon[llmpoon@hku.hk]; Webby, Richard[Richard.Webby@stjude.org]; malik[malik@hku.hk]; Ghazi Kayali[ghazi@human-link.org]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; yguan@hku.hk[yguan@hku.hk]; adolfo.garcia-sastre@mssm.edu['adolfo.garcia-sastre@mssm.edu']; Richard Rothman[rrothma1@jhmi.edu]; Pekosz, Andrew S.[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@stjude.org]; david_topham@urmc.rochester.edu['david_topham@urmc.rochester.edu']; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Perlman, Stanley[stanley-perlman@uiowa.edu]; zhu huachen[zhuhch@hku.hk]; Aubree Gordon[gordonal@umich.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]; PETERPALESE[peter.palese@mssm.edu]; Krammer, Florian[florian.krammer@mssm.edu]; Ben Cowling[bcowling@hku.hk]; larry.anderson@emory.edu[larry.anderson@emory.edu]; jwramme@emory.edu[jwramme@emory.edu]; aneesh.mehta@emory.edu[aneesh.mehta@emory.edu]; Baric, Toni C[antoinette_baric@med.unc.edu]; MASATO HATTA[masato.hatta@wisc.edu]; Gabriele Neumann (gabriele.neumann@wisc.edu)[gabriele.neumann@wisc.edu]; Subbarao, Kanta[kanta.subbarao@influenzacentre.org]; Mathur, Punam (NIH/NIAID) [E][mathurpu@niaid.nih.gov]; Fry, Alicia (CDC/DDID/NCIRD/ID)[agf1@CDC.GOV]; Pallansch, Mark A. (CDC/DDID/NCIRD/DVD)[map1@CDC.GOV]; Hall, Aron (CDC/DDID/NCIRD/DVD)[esg3@CDC.GOV]; Post, Diane (NIH/NIAID) [E][postd@niaid.nih.gov]; Embry, Alan (NIH/NIAID) [E][embrya@niaid.nih.gov]; Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]; Andy Pekosz[apekosz1@jhu.edu]; Topham, David[David_Topham@urmc.rochester.edu]; Gerber, Susan I. (CDC/DDID/NCIRD/DVD)[bhx1@cdc.gov]; zhuhuacher
From: Degrace, Marciela (NIH/NIAID) [E][marciela.degrace@nih.gov]
Sent: Tue 2/11/2020 7:26:57 AM (UTC-05:00)
Subject: RE: virus isolate availability- update

Thanks, Peter. We're going to keep the call and hope some of you at the WHO meeting can join for a bit. I'll also try to send some brief notes after so no one misses any updates on reagent development and availability.

Hope the meeting is going well!!

Marciela

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Tuesday, February 11, 2020 7:14 AM
To: Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov>
Cc: Leo Poon <llmpoon@hku.hk>; Webby, Richard <Richard.Webby@stjude.org>; malik <malik@hku.hk>; Ghazi Kayali <ghazi@human-link.org>; Yoshi Kawaoka <kawaokay@vetmed.wisc.edu>; R.A.M. Fouchier <r.fouchier@erasmusmc.nl>; yguan@hku.hk; adolfo.garcia-sastre@mssm.edu <'adolfo.garcia-sastre@mssm.edu'>; Richard Rothman <rrothma1@jhmi.edu>; Pekosz, Andrew S. <apekosz@jhsph.edu>; Schultz-Cherry, Stacey <Stacey.Schultz-Cherry@stjude.org>; david_topham@urmc.rochester.edu <'david_topham@urmc.rochester.edu'>; Orenstein, Walter <worenst@emory.edu>; Lowen, Anice <anice.lowen@emory.edu>; Baric, Ralph <rbaric@email.unc.edu>; Perlman, Stanley <stanley-perlman@uiowa.edu>; zhu huachen <zhuhch@hku.hk>; Aubree Gordon <gordonal@umich.edu>; Munster, Vincent (NIH/NIAID) [E] <vincent.munster@nih.gov>; PETERPALESE <peter.palese@mssm.edu>; Krammer, Florian <florian.krammer@mssm.edu>; Ben Cowling <bcowling@hku.hk>; larry.anderson@emory.edu; jwramme@emory.edu; aneesh.mehta@emory.edu; Baric, Toni C <antoinette_baric@med.unc.edu>; MASATO HATTA <masato.hatta@wisc.edu>; Gabriele Neumann (gabriele.neumann@wisc.edu) <gabriele.neumann@wisc.edu>; Subbarao, Kanta <kanta.subbarao@influenzacentre.org>; Mathur, Punam (NIH/NIAID) [E] <mathurpu@niaid.nih.gov>; Fry, Alicia (CDC/DDID/NCIRD/ID) <agf1@CDC.GOV>; Pallansch, Mark A. (CDC/DDID/NCIRD/DVD) <map1@CDC.GOV>; Hall, Aron (CDC/DDID/NCIRD/DVD) <esg3@CDC.GOV>; Post, Diane (NIH/NIAID) [E] <postd@niaid.nih.gov>; Embry, Alan (NIH/NIAID) [E] <embrya@niaid.nih.gov>; Lampley, Rebecca (NIH/VRC) [F] <rebecca.lampley@nih.gov>; Stemmy, Erik (NIH/NIAID) [E] <erik.stemmy@nih.gov>; Andy Pekosz <apekosz1@jhu.edu>; Topham, David <David_Topham@urmc.rochester.edu>; Gerber, Susan I. (CDC/DDID/NCIRD/DVD) <bhx1@cdc.gov>; zhuhuachen
Subject: Re: virus isolate availability- update

Some of us are at the WHO R&D Blueprint meeting in Geneva today. I see that Stan Perlman, Kanta Subarrao and others from NIH are in the room. The goal is to set research priorities across everything from animal reservoir to drug/vaccine to social science. We're in breakout groups this afternoon and hopefully can call in for some of the meeting and give a quick update.

Cheers,

Peter

Peter Daszak

(Sent from my iPhone)

President
EcoHealth Alliance

460 West 34th Street, New York, NY10001, USA

www.EcoHealthAlliance.org

On Feb 7, 2020, at 4:49 PM, Degrace, Marciela (NIH/NIAID) [E] <marciela.degrace@nih.gov> wrote:

Hello everyone,

Many of you have asked about availability of virus isolates, and I wanted to provide an update. A 2019-nCoV virus isolate is now available for order in the BEI Resources Repository here: https://www.beiresources.org/Catalog/animalviruses/NR-52281.aspx

Have a great weekend, and looking forward to speaking with you all next Tuesday,

Marciela

-----Original Appointment-----
From: Degrace, Marciela (NIH/NIAID) [E]
Sent: Friday, January 24, 2020 8:08 AM
To: Degrace, Marciela (NIH/NIAID) [E]; Leo Poon; Webby, Richard; malik; Ghazi Kayali; Yoshi Kawaoka; R.A.M. Fouchier; yguan@hku.hk; 'adolfo.garcia-sastre@mssm.edu'; Richard Rothman; Pekosz, Andrew S.; Schultz-Cherry, Stacey; 'david_topham@urmc.rochester.edu'; Orenstein, Walter; Lowen, Anice; Baric, Ralph; 'Perlman, Stanley'; daszak@ecohealthalliance.org; zhu huachen; Aubree Gordon; Munster, Vincent (NIH/NIAID) [E]; PETERPALESE; 'Krammer, Florian'; Ben Cowling; larry.anderson@emory.edu; jwramme@emory.edu; aneesh.mehta@emory.edu; Baric, Toni C; MASATO HATTA; Gabriele Neumann (gabriele.neumann@wisc.edu); Subbarao, Kanta; Mathur, Punam (NIH/NIAID) [E]
Cc: Fry, Alicia (CDC/DDID/NCIRD/ID); Pallansch, Mark A. (CDC/DDID/NCIRD/DVD); Hall, Aron (CDC/DDID/NCIRD/DVD); Post, Diane (NIH/NIAID) [E]; Embry, Alan (NIH/NIAID) [E]; Lampley, Rebecca (NIH/VRC) [F]; Stemmy, Erik (NIH/NIAID) [E]; Andy Pekosz; Topham, David; Gerber, Susan I. (CDC/DDID/NCIRD/DVD); zhuhuachen
Subject: nCoV weekly investigators meeting
When: Tuesday, February 4, 2020 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: GoToWebinar

Hello everyone,

Below please find the registration link for our weekly investigators meeting regarding the nCoV. **Please do not forward**. If you would like anyone else to be added to the invitation, please let me (Marciela.degrace@nih.gov) or Erik (erik.stemmy@nih.gov) know.

Our tentative agendas will be:
- Epi Updates
- NIAID Updates
- Other HHS partner Updates, if applicable
- Investigator research updates
- Discussion and Action Items

Thank you,

Marciela DeGrace, Ph.D.
Project Officer, CEIRS

updated webinar information
https://global.gotomeeting.com/join/

You can also dial in using your phone.
United States: +

Access Code:

To: Degrace, Marciela (NIH/NIAID) [E][marciela.degrace@nih.gov]; Leo Poon[llmpoon@hku.hk]; Webby, Richard[Richard.Webby@STJUDE.ORG]; malik[malik@hku.hk]; Ghazi Kayali[ghazi@human-link.org]; Yoshi Kawaoka[kawaokay@vetmed.wisc.edu]; R.A.M. Fouchier[r.fouchier@erasmusmc.nl]; yguan@hku.hk[yguan@hku.hk]; Richard Rothman[rrothma1@jhmi.edu]; Pekosz, Andrew S.[apekosz@jhsph.edu]; Schultz-Cherry, Stacey[Stacey.Schultz-Cherry@STJUDE.ORG]; Orenstein, Walter[worenst@emory.edu]; Lowen, Anice[anice.lowen@emory.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'Perlman, Stanley'[stanley-perlman@uiowa.edu]; daszak@ecohealthalliance.org[daszak@ecohealthalliance.org]; zhu huachen[zhuhch@hku.hk]; Aubree Gordon[gordonal@umich.edu]; Munster, Vincent (NIH/NIAID) [E][vincent.munster@nih.gov]; Palese, Peter[peter.palese@mssm.edu]; Ben Cowling[bcowling@hku.hk]; larry.anderson@emory.edu[larry.anderson@emory.edu]; jwramme@emory.edu[jwramme@emory.edu]; aneesh.mehta@emory.edu[aneesh.mehta@emory.edu]; Baric, Toni C[antoinette_baric@med.unc.edu]; MASATO HATTA[masato.hatta@wisc.edu]; Gabriele Neumann (gabriele.neumann@wisc.edu)[gabriele.neumann@wisc.edu]; Subbarao, Kanta[kanta.subbarao@influenzacentre.org]; Garcia-Sastre, Adolfo[Adolfo.Garcia-Sastre@mssm.edu]; Matthew Frieman[matt.frieman@gmail.com]
Cc: Fry, Alicia (CDC/DDID/NCIRD/ID)[agf1@CDC.GOV]; Pallansch, Mark A. (CDC/DDID/NCIRD/DVD)[map1@CDC.GOV]; Hall, Aron (CDC/DDID/NCIRD/DVD)[esg3@CDC.GOV]; Post, Diane (NIH/NIAID) [E][postd@niaid.nih.gov]; Embry, Alan (NIH/NIAID) [E][embrya@niaid.nih.gov]; Lampley, Rebecca (NIH/VRC) [F][rebecca.lampley@nih.gov]; Stemmy, Erik (NIH/NIAID) [E][erik.stemmy@nih.gov]; Andy Pekosz[apekosz1@jhu.edu]; Topham, David[David_Topham@URMC.Rochester.edu]; Gerber, Susan I. (CDC/DDID/NCIRD/DVD)[bhx1@cdc.gov]; zhuhuachen
From: Krammer, Florian[florian.krammer@mssm.edu]
Sent: Tue 2/11/2020 4:56:55 PM (UTC-05:00)
Subject: Re: nCoV weekly investigators meeting

Dear all,

A paper describing the pathogenicity of SARS CoV 2 (aka nCoV) in hACE2 mice just came out in Bioarchive: https://www.biorxiv.org/content/10.1101/2020.02.07.939389v1.full.pdf

Best,

Florian

From: Degrace, Marciela (NIH/NIAID) [E]
Sent: Friday, January 24, 2020 8:08 AM
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Subject: nCoV weekly investigators meeting
When: Tuesday, February 11, 2020 9:00 AM-10:00 AM.
Where: GoToWebinar

USE CAUTION: External Message.

Hi everyone,
Please see updated webinar links below. Hopefully this resolves any issues people had last time with sound.
Hello everyone,
Below please find the registration link for our weekly investigators meeting regarding the nCoV. **Please do not forward**. If you would like anyone else to be added to the invitation, please let me (Marciela.degrace@nih.gov) or Erik (erik.stemmy@nih.gov)

know.
Our tentative agendas will be:

- Epi Updates
- NIAID Updates
- Other HHS partner Updates, if applicable
- Investigator research updates
- Discussion and Action Items

•

updated webinar link
https://global.gotomeeting.com/join/

You can also dial in using your phone.
United States:

Access Code:
Thank you,
Marciela DeGrace, Ph.D.
Project Officer, CEIRS
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Subject: nCoV investigator call - follow up resources
200_Protocol_v28_0.pdf

Hi everyone,

It was great speaking to you yesterday. Thank you for sharing your updates. As promised, here's some information for those unable to join yesterday's call so you can stay in the loop.

Funding: While we currently do not have any new funds designated for nCoV, we are collecting supplement requests so we can be ready if/when funds arrive.

Grantees: To submit a supplement request, please follow the instructions of this NOSI. The appropriate PA to use for submission is here.

CEIRS: Please send the CEIRS concept form to me and to the Prime PI of the Center you are working with.

If you are currently funded by CEIRS and have an urgent need for nCoV funds, write me an email and we can discuss. If you have both CEIRS and grant funding, please do not submit the same work to both as we will be reviewing all requests together.

Reagents: Currently BEI has one virus isolate available and is working on making genomic RNA available. We're also aware that the European Virus archive has an isolate and RNA. We are trying to get more isolates from multiple countries into BEI – please keep me informed if you know of connections we can reach out to about this. As you develop reagents, Erik and I will work with you to help expedite their deposit into BEI, so please keep us posted on your progress.

We are also working to see if the Ad-ACE2 vector can be deposited and I'll try to update by next week. If there are other high priority reagents you would like to see in BEI, please email me so I can curate a list.

Patient Samples: CDC teams still working on outreach and consent, so we expect an extremely limited supply of PBMCs, sera and blood from US patients. For those interested in setting up a protocol for collection of samples from patients at their institution or with a collaborator abroad, a template that the NIH Vaccine Research Center uses is attached. Please keep Erik and I informed if you decide to pursue this.

Thank you all! Please don't hesitate to email with any questions and we will talk next Tuesday! Looking forward to updates from those of you doing animal model testing.

Marciela

Version 28.0
March 19, 2019

Vaccine Research Center
VRC 200
(03-I-0263)

A Multicenter Specimen Collection Protocol to Obtain Human Biological Samples for Research Studies

Protocol Sponsored by:

Vaccine Research Center (VRC)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Bethesda, Maryland

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TABLE OF ABBREVIATIONS

AE	Adverse Event
CBC	Complete Blood Count
CD4	Cluster of Differentiation Antigen 4
CLIA	Clinical Laboratory Improvement Act
DTM	Department of Transfusion Medicine
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRPP	Human Research Protection Program
IoR	Investigator of Record / Site Principle Investigator
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PBMCs	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
UP	Unanticipated Problem
VITL	Vaccine Immunology Testing Laboratory
VRC	Vaccine Research Center
WBC	White Blood Cell

PRÉCIS

VRC 200: A Multicenter Specimen Collection Protocol to Obtain Human Biological Specimens for Research Studies

Protocol Design: This protocol is designed to perform collection of human specimens, such as blood, mucosal secretions, skin swabs, skin biopsy, or body fluids to support research studies. These samples will be used by researchers in their work on the development of vaccines, to study the correlates of immunity related to infectious diseases and in laboratory work related to the development and/or validation of immunological assays. Standard phlebotomy and apheresis procedures will be utilized to safely obtain necessary quantities of blood and cells.

Subjects: Adults ages 18 years and older.

Protocol Plan: Subjects who consent to participate will undergo standard medical procedures to obtain biological specimens. The signed informed consent is valid for one year; at least once per year, the subject must re-consent and eligibility should be re-confirmed.

Duration: Individual subjects may donate samples as often as permitted by their institution's guidelines. The IRB-approved protocol will remain open and undergo annual continuing review by the IRB as long as there continues to be a need for human biological specimens for research studies.

Endpoints: There is no analysis plan for this protocol. This protocol will be conducted in accordance with Good Clinical Practices for human research solely for the purpose of obtaining samples for research laboratories. Samples will be identified only by protocol identification number. Subject data, such as demographic information, aspects of medical history, laboratory parameters, recent immunizations or medications, HLA type, genetic tests and other medical information may be provided (identified by study number, but not subject name) to researchers if needed to support the objectives of the laboratory research.

1. INTRODUCTION AND RATIONALE

Research at the Vaccine Research Center (VRC) is ongoing to investigate different aspects of HIV and other infectious diseases as well as to elucidate human immunology. Frequently these laboratory studies require serum, plasma, peripheral blood mononuclear cells (PBMCs) and other types of human biological specimens, such as mucosal secretions (collected by swabs), body fluids, skin swabs or skin biopsy. This protocol allows for subjects to undergo a variety of routine specimen collection procedures to obtain biological samples that will be used by laboratory researchers in their work to develop vaccines and monoclonal antibodies, to study the correlates of immunity related to infectious diseases, and to develop and/or validate immunological assays.

2. DESCRIPTION OF SPECIMEN COLLECTION PROCEDURES

2.1 Specimen Collection Procedures

Specimens will be obtained by routine medical practice methods.

- Blood samples will be collected from a vein by standard phlebotomy techniques.
- Body fluid samples including urine, semen, saliva, skin swabs, and/or mucosal secretions will be collected by standard clinical techniques. Mucosal secretions that may be collected include nasal, oral, pharyngeal, aural, conjunctival, vaginal, cervical, rectal and penile secretions.
- Skin biopsy samples will be collected by standard biopsy technique using local anesthesia. If a subject is willing to undergo a skin biopsy, then a separate consent process for this procedure will be completed. The sample collected will not routinely be sent for a formal pathology review, but may be sent at the discretion of the clinician if there is suspicion of an undiagnosed condition.

The results of testing performed by research laboratories will not be part of the subject's medical record. This protocol alone is not intended for general longitudinal study of subjects.

Specimens collected for standard diagnostic testing (e.g., swab for diagnosis of a skin infection, urine for pregnancy testing/urinalysis, blood for HIV testing, complete blood count, chemistry panel, lipid panel, hepatic panel, hepatitis screening, PT, PTT, HLA and lymphocyte phenotyping) may be collected for documentation of medical status when needed to either support a research project or assess well-being of the subject with regard to undergoing sample collection procedures. Results of such tests are available in the subject's medical record. Other standard medical tests may be obtained as well. Study subjects will be informed of any results that suggest a new diagnosis.

2.2 Apheresis Procedures at NIH

Each apheresis procedure will be carried out by trained members of the NIH Clinical Center Apheresis Clinic under the supervision of the medical staff of the Department of Transfusion Medicine (DTM) by recommended methods [1]. Apheresis will be done using devices and procedures that conform to standard DTM guidelines and Standard Operating Procedures (SOPs). The plasma or peripheral blood mononuclear cells (PBMCs), or both, as requested, will be harvested. The red blood cells will be returned to the subject during all procedures and the plasma will be returned when PBMCs alone are the collected sample.

Blood from apheresis donors may also be tested for hepatitis A-G as part of the research investigation. HLA typing, genetic tests and HIV testing may also be performed. Stored samples may be used later to further evaluate immune responses and to elucidate genetic factors associated with immune response.

Approximately 1.0 – 3.0 x 10^9 cells will be collected per lymphapheresis procedure. The interval between successive apheresis procedures should be 21 or more days. In addition, the following guidelines apply to HIV positive subjects:

a) Subjects with CD4 <200 cells/μL are restricted to 3 apheresis sessions/year.
b) Subjects with CD4 >200 cells/μL are restricted to 6 apheresis sessions/year.

Subjects may be asked to undergo repetitive apheresis procedures depending upon the requirements of the particular research project for which the cells or plasma are being collected. Except under special circumstances (i.e. to be decided on a case-by-case basis), no subject should be asked to undergo more than six procedures per year. The DTM omnibus protocol for collection of mononuclear cells for research use by NIH investigators (protocol #99-CC-0168) allows performance of leukapheresis every 3 weeks in healthy subjects, not to exceed 17 donations per year. The U.S. Food and Drug Administration (FDA) regulations allow cytapheresis donations at a frequency of 24 donations per year, and plasmapheresis donations twice weekly [2]. With appropriate monitoring, at these frequencies, no detrimental long-term effects on healthy donors have been documented [3-6]. Since some of the subjects on the current protocol will have HIV infection, a more conservative upper limit of six donations per year was chosen.

Physicians or other staff ordering serial apheresis procedures are responsible for monitoring the immunologic and hematologic parameters of the subjects during these procedures. Declines in CD4 count, platelet counts, etc. that are potentially procedure-related will be considered when scheduling the interval for a subsequent apheresis procedure.

All exceptions to the above guidelines need to be discussed with and cleared by the PI (or designee) and must be reviewed and approved by the NIAID IRB beforehand. Apheresis of subjects in violation of the above guidelines may result in loss of access to this protocol.

2.3 Apheresis Procedures at External Research Sites

If an apheresis procedure is performed at other sites outside of NIH, local site SOPs and guidelines will be followed.

3. PROTOCOL OBJECTIVES

To obtain human biological specimens such as blood (via phlebotomy), plasma or PBMC samples (via apheresis), mucosal secretions, skin swabs, body fluids or skin biopsy to support medical research.

4. PROTOCOL DESIGN AND CLINICAL PROCEDURES

Informed consent using a site-specific IRB-approved informed consent form will be obtained by all subjects prior to participation in this protocol. This protocol also allows for remote enrollment and sample collection, with the option for remote informed consent process being conducted by telephone (see Appendix IV).

4.1 Eligibility Criteria

Criteria for enrollment are minimal; however, additional eligibility requirements will be confirmed by a study clinician before scheduling a subject for apheresis or skin biopsy.

4.1.1 Inclusion Criteria

A subject must meet all of the inclusion criteria, as follows:

1. Age 18 years or older
2. Able and willing to complete the informed consent process
3. Willing to provide blood or other samples that will be stored for future research
4. Able to provide proof of identity to the acceptance of the clinician completing the enrollment process; when the telephone consent process is used, the clinician performing the sample collection will review and confirm the proof of identity

4.1.2 Exclusion Criteria

A subject will be excluded from protocol participation if there is presence of a condition that the attending physician considers to be a contraindication to the specimen collection procedures.

4.2 Screening and Annual Eligibility Visits

Prescreening will include education about study procedures and a discussion of the eligibility criteria and purpose of the sample collections. If the subject is willing to participate, the informed consent will be signed and eligibility criteria documented. Subjects can participate in this protocol for one year using a single consent document. The informed consent will be reviewed and signed again if it has been more than one per year since the last prior specimen collection.

Screening evaluations that are required for determining specimen collection procedural eligibility must be completed within the 56 days prior to the procedure being performed. If the required evaluations are already available in the subject's medical record within the required timeframe, they do not have to be repeated for this protocol.

Screening and specimen collection procedures may all be performed in one visit or may be split into more than one visit, as needed, to meet the needs of an individual subject or the research study.

4.2.1 Schedule of Evaluations

1. Informed Consent process and signature of consent
2. Medical History; this may be limited to information relevant to the sample collection procedures or laboratory research for which the sample will be used. If a skin biopsy is to be collected, then the subject will be asked about a history of keloid scar formation and allergies to local anesthetic medications.
3. Physical Examination; this may be limited to blood pressure, temperature, heart rate, height and weight. A more extensive physical exam is not required, but may be performed based on the medical judgment of the clinician completing the screening process, needs of the research for which the sample is being collected or if requested by the subject.

4. CBC with differential and platelets: This evaluation is typically done but may be deemed as "not required" by a study physician or advanced practitioner based upon the circumstances and type of sample collection.
5. HIV-1 Serology: This evaluation is typically done as an HIV ELISA, with confirmatory testing needed to document HIV status; sites may use HIV tests that meet local institutional policy.

   For subjects already documented in the medical record to be HIV positive a quantitative viral load measurement alone may be done. When HIV status is not considered relevant to the research sample use, it is not a required evaluation.
6. CD4 count is optional, but usually obtained for subjects already documented in the medical record to be HIV positive; CD4 count may be done, but is not required for other study subjects.
7. Collection of samples to be stored for subsequent testing for hepatitis, other pathogens, and/or genetic tests/HLA type if needed for research use of the sample.
8. Other laboratory tests, as needed, to provide medical status information to support the research study or to assess the subject's well-being.

4.3 APHERESIS

In order to undergo apheresis procedures, a subject must have no medical contraindications. All apheresis procedures performed under this protocol are solely for research purposes. Subjects participating in an active clinical research protocol may participate in the apheresis protocol if the total amount of blood drawn does not exceed NIH guidelines or a site's institutional guidelines. A study clinician will complete a checklist for apheresis eligibility before referring a subject for apheresis. At the NIH, prior to scheduled procedure, the subject must have a venous assessment performed by the Apheresis staff to determine suitability for apheresis.

4.3.1 Apheresis Eligibility Criteria

For Healthy Volunteer

A healthy volunteer must meet all of the following criteria:

1. Afebrile (temperature $\leq 37.5^0$C)
2. Weight $\geq$110 pounds
3. Adequate bilateral antecubital venous access
4. Hemoglobin $\geq$ 12.5 g/dL for females; $\geq$ 13.0 g/dL for men
5. Platelets > 150,000 K/uL
6. No cardiovascular instability as indicated by a) history of medically significant cardiac arrhythmia within the last 12 months, or b) ischemic cardiovascular disease within the last 12 months, or c) heart rate outside of the 50 - 100 beats/minute interval (on 3 successive readings), or d) blood pressure greater than 180 mmHg (systolic) or 100 mmHg (diastolic) on 3 successive readings
7. No current lung or kidney disease
8. No known coagulation disorder

9. No sickle cell disease
10. No active or chronic hepatitis
11. No intravenous injection drug use in the past 5 years
12. Not breast feeding
13. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum) performed by a VRC study clinician within 72 hours prior to the apheresis procedure

Infectious Disease Patient

A patient with an infectious disease must meet all of the following criteria:

1. Weight ≥ 110 pounds
2. Afebrile (temperature ≤ 37.5° C)
3. Adequate bilateral antecubital venous access
4. No cardiovascular instability as indicated by a) history of medically significant cardiac arrhythmia within the last 12 months, or b) ischemic cardiovascular disease within the last 12 months, or c) heart rate outside of the 50 - 100 beats/minute (on 3 successive readings), or d) blood pressure greater than 180/100 mmHg (on 3 successive readings)
5. No current lung or kidney disease
6. No known coagulation disorder
7. No receipt of clotting factor concentrates in the past 5 years
8. Hemoglobin ≥ 9.0 g/dL
9. Platelets ≥50,000 K/uL
10. WBC ≥ 2.0 K/uL
11. Not breast feeding
12. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum) performed by a VRC study clinician within 72 hours prior to the apheresis procedure

4.3.2 Apheresis Procedures

Subjects must have initial apheresis procedure within 56 days of eligibility screening. Once determined eligible for apheresis, subjects do not need to be re-screened for each subsequent apheresis procedure unless deferred by the apheresis unit.

For women of reproductive potential, a pregnancy test by blood or urine will be performed by a VRC study clinician within 72 hours prior to the apheresis procedure. Results must be negative to proceed with apheresis.

Prior to beginning the apheresis procedure, a study clinician may request in advance that other laboratory tests be collected, such as CD4+ T cell count, PCR viral load, liver function panel or other tests as needed to monitor the well-being of the subjects or samples as needed by a research laboratory. The total volume of blood samples and types of specimens collected will be recorded in the records kept for each protocol visit.

Apheresis will require two antecubital venous access sites and will involve processing of less or equal to 5 liters of whole blood. When PBMC are collected, the expected mononuclear cell yield is approximately 0.5 to 1.0 x 10^9 cells per liter processed, and the apheresis device can process about 2-3 liters per hour. Thus, 1 to 2 hours are required to process 1 to 4 liters of blood and obtain about 1 to 4 x 10^9 leukocytes.

The volume of plasma removed during an apheresis procedure may range from 100 to 600 mL, depending on the procedure. The plasma volume is not replaced per regulatory standards. Subjects will be advised to drink a 12-oz glass of a decaffeinated beverage prior to the procedure.

About 6 mL of red blood cells will also be lost through the apheresis procedure. To account for this, a volume of 6 mL will be included when calculating the total whole blood sample volumes collected per apheresis visit. The clinic staff will take into account all samples collected for this and other protocols in which the subject may be participating.

During or following an apheresis visit, if there is any concern about the well-being of the subject, the clinic may conduct appropriate medical evaluations by history-taking, physical examination, laboratory tests, and/ or other testing.

NIH Clinic Site only:

All study subjects will be treated according to standard whole blood and apheresis donation policies and procedures operative in the Department of Transfusion Medicine (DTM). The Dowling Apheresis Clinic staff at the NIH Clinical Center routinely performs a hemoglobin test prior to initiating apheresis. If a subject is found to have a hemoglobin value less than permitted by the Apheresis Clinic, then the apheresis will not be initiated and the ordering provider will be notified. The VRC Study Coordinator will provide the Apheresis center with a request for numbers and types of tubes of blood to be collected prior to beginning the apheresis.

4.4 Skin Biopsy

The skin biopsies will be performed by a trained professional under universal antiseptic norms. The procedure may be done using local anesthesia. In order to undergo a skin biopsy, a subject must have no medical contraindications. The clinician will complete a checklist for skin biopsy eligibility before the procedure is performed. The skin biopsy eligibility includes the following:

1. No known allergies to the local anesthetic to be used
2. No history of keloid formation
3. No known coagulation disorders
4. Not pregnant or breast feeding

Subjects will have no more than 2 skin biopsies in the same visit and no more than 6 biopsies in a 1-year period.

Formal pathology review in a CLIA certified laboratory will not be performed unless the clinician assesses that there may be a medical condition not previously diagnosed.

4.5 Body Fluid Samples

For males providing a semen specimen in clinic, a private room will be given for the donation. Semen will be collected into a clinical container made for this purpose.

Urine samples, oral secretions, swabs of mucosa (e.g. gingiva, pharynx, penis, rectum, vagina) will be collected by standard clinical techniques.

These samples may be used for routine clinical testing or delivered to investigators or collaborators for research assays or storage for future research.

4.6 Criteria for Discontinuing Participation

A subject may be discontinued from protocol participation for the following reasons:

1. Subject decides to discontinue participation
2. Subject has not had any protocol visits for 1 year
3. Subject has a serious adverse event related to study procedures that is a contraindication to future specimen collection procedures
4. Subject develops a medical condition that is a contraindication to continuing study participation
5. Subject becomes pregnant
6. Subject has repeatedly fails to comply with protocol requirements
7. The site Principal Investigator, Protocol Chair, or IRB decide to stop the protocol
8. The site Principal Investigator or Protocol Chair assesses that it is not in the best interest of the subject for the subject to continue participation

Subjects discontinued from participation may return to active status at a later date provided they are determined to be eligible by undergoing the screening process again and signing a new consent. Such subjects should be returned to active status using the same study identification number assigned previously for this protocol.

4.7 Criteria for Stopping the Protocol

This study will be stopped if the Investigators decide that no additional subjects are needed or if regulatory authorities require discontinuation of the study.

5. SAFETY AND EVENT REPORTING

5.1 Definitions

5.1.1 Adverse Event

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

The risks of the study procedures are minimal and are generally confined to the period of the actual study visit itself. In this protocol, AEs that are non-serious will not be routinely recorded in the protocol database.

5.1.2 Serious Adverse Event

An AE is designated a Serious Adverse Event (SAE) if it has any of the following outcomes:

- results in death;
- is life-threatening (i.e., places the subject at immediate risk of death);
- results in inpatient hospitalization or prolongation of an existing hospitalization;
- results in a congenital anomaly/birth defect; **or**
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above in this definition

For this sample collection protocol, only SAEs that occur during or within 24 hours after a protocol visit will be recorded in the study database. In this regard, the outcome of any pregnancies identified during participation in this screening protocol will **not** be followed for collection of data about possible congenital anomalies or birth defects as there are no investigational treatments or procedures associated with this screening protocol.

5.1.3 Unanticipated Problem

An Unanticipated Problem (UP) is defined as any incident, experience, or outcome that meets **all three** of the following criteria:

- is unexpected in nature, severity, or frequency in relation to the research risks that are described in the protocol, informed consent, Investigator's Brochure, other study documents or in consideration of the characteristics of the subject population being studied; **and**
- is related to participation in the research; **and**
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious UP: An UP that meets the definition of an SAE or compromises the safety, welfare or rights of subjects or others.

An UP that is not an AE (UPnonAE) is an UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, for this study, we will report occurrences of breaches of confidentiality or accidental destruction of study records.

5.1.4 Protocol Deviation Definition

A Protocol Deviation is defined as any change, divergence, or departure from the IRB-approved study procedures in a research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

Non-serious Protocol deviations are characterized as:

- Those that occur because a member of the research team deviates from the protocol.
- Those that are identified before they occur, but cannot be prevented.
- Those that are discovered after they occur.

Serious Protocol Deviation: A deviation that meets the definition of a SAE or compromises the safety, welfare or rights of subjects or others.

5.1.5 Non-Compliance Definition

Non-compliance is the failure to comply with applicable NIH HRPP policies, IRB requirements, site-specific regulatory requirements or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as serious, continuing or minor.

"Serious non-compliance" is defined as non-compliance that:

- Increases risks, or causes harm, to participants
- Decreases potential benefits to participants
- Compromises the integrity of the NIH-HRPP
- Invalidates the study data

"Continuing non-compliance" is non-compliance that is recurring.

"Minor non-compliance" is non-compliance that is neither serious nor continuing.

5.2 Reporting to the NIAID IRB

Refer to the NIAID IRB website for the forms, procedures and most current guidance to use when reporting to the IRB.

The following will be reported within 7 calendar days of investigator awareness:

- Serious and non-serious UP
- Deaths
- Serious protocol deviations
- Serious or continuing non-compliance
- SAEs that are possibly, probably, or definitely related to the research regardless of expectedness. Only SAEs that occur during or within 24 hours after the protocol visit will be reported.

The following waiver applies to reporting anticipated protocol deviations and expected UPnonAEs: Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected AEs will not be reported to the IRB unless they occur at a rate greater than that known to occur in healthy adults. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems.

5.2.1 Annual Reporting to the IRB

The following will be reported to the IRB in summary at the time of Continuing Review:

- Serious and non-serious UP
- Expected SAEs that are possibly, probably, or definitely related to the research
- SAEs that are not related to the research
- All AEs, except expected AEs granted a waiver of reporting
- Serious and Non-Serious Protocol Deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

5.3 Reporting to a non-NIH IRB

Each site IoR is responsible for reporting AEs, unanticipated problems, protocol deviations and non-compliance to the site IRB and other relevant local regulatory authorities in accordance with their institutional and country requirements for reporting.

Site-specific data reports will be made available through the data management contractor to facilitate expedited and continuing review reporting requirements.

5.4 Data and Safety Monitoring Plan

The risk level of this protocol is low. The Principal Investigator and designees will monitor study data and subject safety.

6. STATISTICAL CONSIDERATIONS

This protocol does not require a statistical endpoint analysis. Data and blood samples collected as part of the protocol will be provided to laboratory investigators as needed for laboratory research analyses in a manner that does not reveal the identity of the subject.

7. STORED SAMPLES, HEPATITIS AND HIV SCREENING, AND GENETIC TESTING

To be eligible for the protocol, participants must be willing to allow stored specimens to be used in the future for studying HIV disease, immune function, and other medical conditions, and to have viral hepatitis screening, HIV testing, and genetic tests, including HLA typing, performed. If tests show evidence of any acute or chronic condition, subjects will be informed of the results and advised to seek appropriate medical care for the condition.

<u>Intended use of the samples/specimens/data</u>:

Samples, specimens and data collected under this protocol may be used to study HIV and other diseases, the immune system, other medical conditions, and for research assay validation. Genetic testing may be performed in accordance with the genetic testing information that was included in the study informed consent.

<u>How stored samples, specimens and data from sample use will be stored</u>:

All of the stored study research samples are labeled by a code (such as a number) that only the study team can link to the subject. Samples are stored at the Vaccine Immunology Testing Laboratory (VITL) in Gaithersburg, MD, at VRC laboratories, or at approved research

collaborator laboratories, which are all secure facilities with limited access. Skin biopsy samples collected for research may be stored at an approved collaborating laboratory (refer to Appendix II). Data will be kept in password-protected computers. Only investigators or their designees will have access to the stored samples and data.

How samples/specimens/data will be tracked:

Samples used by VITL will be tracked in the Laboratory Information Management System (LIMS) database. Research samples collected at each study visit will be recorded in the Advantage EDC database.

What will happen to the samples/specimens/data at the completion of the protocol:

In the future, other investigators (both at NIH and at external sites) may wish to study these samples and/or data. IRB approval must be sought prior to any sharing of samples. Any clinical information shared about those samples would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research, which is authorized to determine whether a research activity is exempt.

At the time of protocol termination, samples will remain in the VITL facility, VRC laboratories or approved collaborator's laboratory (refer to Appendix II). With IRB approval, stored samples may be transferred to another repository. Data will be archived by the VRC in compliance with regulatory requirements for retention of research records, or after IRB approval, records may be either destroyed or transferred to another repository.

Circumstances that would prompt the PI to report loss or destruction of samples/specimens/data to the IRB:

The NIH Intramural Protocol Violation definition related to loss of or destruction of samples will be followed in reporting to the IRB. Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that compromises the scientific integrity of the study will be reported to the IRB. The PI will also notify the IRB if the decision is made to destroy the remaining samples.

8. HUMAN SUBJECT PROTECTIONS

This research study will be conducted in compliance with the protocol, Good Clinical Practices (GCP), and all applicable regulatory requirements.

8.1 INSTITUTIONAL REVIEW BOARD

A copy of the protocol, proposed informed consent document, other written information that is given to subjects, and any proposed advertising material will be submitted to the IRB for written approval.

The investigator will submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator will notify the IRB of deviations from the protocol or serious AEs occurring at the site and other AE reports received from NIAID, VRC, in accordance with local procedures. The investigator will be responsible for obtaining annual IRB approval/renewal throughout the duration of the protocol.

8.2 Subject Identification and Enrollment of Subjects

Participants may be subjects participating solely in this protocol or may be subjects in other VRC studies from whom more cells are needed for research than can be collected by routine phlebotomy. This is not research protocol that requires a fixed schedule of evaluations or a population in which all participants have particular health characteristics in common.

8.2.1 Participation of Children

Children are not eligible to participate in this clinical trial. The guidelines for the participation of children are in 45 CFR 46, Subpart D, 401-409. Under the Department of Health and Human Services protections for children, generally, healthy children can be studied when the research is considered as "not greater than minimal risk." Children can be involved in research with greater than minimal risk only when it presents the prospect of direct benefit to the individual child or is likely to yield generalizable knowledge about the child's disorder or condition.

8.2.2 Participation of Site Employees

Each study site will follow institutional policies regarding participation of site employees in VRC 200. Site specific policies related to employee involvement in research protocols have been provided to NIAID IRB.

NIH Clinic Site Specific:

At the VRC site, NIH employees and members of their immediate families may participate in this protocol. The VRC site will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the “NIH Information Sheet on Employee Research Participation” and a copy of the “Leave Policy for NIH Employees Participating in NIH Medical Research Studies.”

Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant’s employment or work situation. The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees. The employee subject’s privacy and confidentiality will be preserved in accordance with NIH Clinical Center and NIAID policies. For the NIH employee subjects, consent will be obtained by an individual who is independent of the employee’s team. If the individual obtaining consent is a co-worker to the subject, independent monitoring of the consent process will be included through the Bioethics Consultation Service. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

University of Puerto Rico Medical Sciences Campus (UPR MSC) Site Specific:

At the UPR MSC site, UPR MSC employees and students will not be enrolled in this protocol. The UPR MSC site will only enroll subjects from the community.

8.3 Informed Consent

The study informed consent form template is provided in Appendix I. The written informed consent document should be prepared in the language(s) of the potential subject population. Before a subject’s participation in the protocol, it is the investigator’s responsibility to ensure that written informed consent is obtained from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the protocol and before any protocol-specific screening procedures.

The acquisition of informed consent should be documented in the subject's medical records, as required by 45 CFR 46.117 and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent document should be retained in the medical chart and a copy of the consent form should be provided to the subject.

8.4 SUBJECT CONFIDENTIALITY

The investigator will ensure that the subject's anonymity is maintained in any reports. All records will be kept confidential to the extent provided by federal, state and local law. Medical records are made available for review within the guidelines set by the Federal Privacy Act. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the protocol.

8.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

There is no benefit to the subject for participating in this protocol, but society may benefit from knowledge gained from research on the specimen donations.

Risks of Specimen Collections: All specimen collection procedures used are common in routine medical practice.

- *Blood drawing*: The risks of blood sample collection are minimal and consist of mild discomfort at the sample collection site. The procedure may cause pain, bruising, and, rarely, infection at the site where the blood is taken.
- *Collection of samples by swabs*: rubbing swabs over the mucosal surfaces can cause momentary discomfort.
- *Skin biopsy*: any time the skin is opened, such as occurs with a skin biopsy, there is a chance of infection. Infection after a skin biopsy is rare and care will be taken to try to prevent infection. There may be pain or discomfort during the skin biopsy or while it is healing. There may be a small amount of bleeding after the skin biopsy. There is the risk of a small scar. Subjects known to form "keloid" scars are not eligible for a skin biopsy performed solely for research purposes. Rarely, the local anesthetic medicine used to numb the skin may cause an allergic reaction.
- *Apheresis*: donations may cause pain, bruising, and discomfort in the arms where the needles are placed. It may also cause chills, nausea, heartburn, mild muscle cramps and tingling sensation around the mouth or in the fingers, however this can usually be relieved by slowing or temporarily interrupting the apheresis or taking a calcium containing antacid, such as Tums®. Other possible side effects are anxiety, vomiting and lightheadedness. Temporary lowering of the blood pressure may develop. There is the rare possibility of infection, fainting or seizure. Very rarely a nerve problem at the needle placement site may occur. Also, very rarely, a machine malfunction may occur, resulting in the loss of about one unit of blood. There may be additional risks of apheresis that are unknown at this time.
- *New Diagnoses*: It is possible that the standard medical tests performed as part of this research protocol will result in new diagnoses. Depending upon the medical findings and

consequences of being provided with the new medical information about health status, the study subject may view this aspect of study participation as either a risk or a benefit.

Expected Adverse Events Associated with Apheresis:

All study subjects will be treated according to standard whole blood and apheresis donation policies and procedures operative in the DTM. Adverse reactions to apheresis procedures are rare. They include pain and bruising at needle placement sites and the loss of less than a pint of blood due to rare cases of apheresis device malfunction. Vasovagal episodes, characterized by transient hypotension, dizziness, nausea, and rarely syncope, are seen in less than 5% of procedures. Citrate toxicity, consisting of cutaneous paresthesia's, chills, nausea, and rarely muscle spasms, is caused by the citrate anticoagulant used to prevent the extracorporeal circuit from clotting, and may be seen to a mild degree in 30-50% of donations. Postural manipulation and fluid administration are used to manage vasovagal reactions. Citrate reactions are usually relieved by slowing the rate of the anticoagulant infusion and by administering oral calcium carbonate tablets.

The plastic kits used to collect the blood and apheresis products are sterilized, single-use, disposable sets. No blood products are given during these donations and procedures. A DTM physician is available in or near the Apheresis Donor Area at all times to provide short term medical care for complications or reactions resulting from the donation procedures.

Rarely, machine malfunction may results in loss of as much as a half-unit (250 mL) of whole blood.

Subjects may rarely sustain a drop in total lymphocyte count (and CD4+ T cell count) when lymphapheresis is performed frequently over a short period of time[5, 6]. The extent and duration of this drop appears to be variable and not necessarily predictable; therefore there are no absolute guidelines as to what may constitute an excessive number or frequency of procedures under these circumstances. Further, the long-term consequences, if any, of this drop are unknown, but presumably could be more significant in subjects with pre-existing baseline abnormalities in total lymphocyte or CD4+ T cell numbers, such as those with advanced HIV-1 disease or other causes of lymphocytopenia. As a safeguard, the Apheresis Clinic has guidelines to assist in determining whether it is both safe and appropriate for a given subject to undergo serial apheresis procedures. However, these guidelines are general rules that are not meant to take the place of the clinical judgment of the Principal Investigator in reviewing a subject's clinical history and deciding independently whether a subject remains eligible to undergo additional apheresis procedures. Individual scientists or other protocol personnel requesting apheresis of particular subjects are also responsible for ensuring that serial measurements of CD4+ T cell counts, platelet numbers, and other safety parameters as indicated, are performed appropriately. This is particularly important if individual subjects are having apheresis procedures performed for more than one research protocol.

8.6 COMPENSATION

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation at each site. The total compensation for the subject is based on the number of study clinic visits and sample collections performed.

Compensation rates are based on site policy and are consistent with similar protocols conducted at these sites. Sites rates are as follows:

Site	Apheresis Procedures	Clinic Visits Involving Needle-stick Procedures (excluding apheresis)	Clinic Visits Without Needle-stick Procedures	Skin Biopsy	Timeline for providing compensation
VRC	$250	$175	$75	$200	After each completed clinic visit by direct deposit
UPR MSC	N/A	$100	$50	N/A	After each completed clinic visit by cash

The approximate total compensation is included in each site informed consent document. Compensation may need to be reported to the Internal Revenue Service (IRS) as taxable income.

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 PROTOCOL DOCUMENTATION AND STORAGE

The principal investigator will maintain a list of appropriately qualified persons to whom trial duties are delegated.

Source documents are original documents, data, and records from which the subject's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, and correspondence.

The investigator and staff are responsible for maintaining a comprehensive and centralized filing system of all protocol-related essential documentation, suitable for inspection at any time by representatives from NIAID, VRC and/or applicable regulatory authorities. Elements include:

- Subject files containing completed informed consent documents, and supporting copies of source documentation
- Files containing the protocol with all amendments, copies of all correspondence with the IRB and the National Institute of Allergy and Infectious Diseases, Vaccine Research Center.

In addition, all original source documentation will be maintained and be readily available.

All essential documentation will be retained by the institution for the same period of time required for medical records retention. No protocol document will be destroyed without prior written agreement between the National Institute of Allergy and Infectious Diseases, Vaccine Research Center and the investigator.

9.2 Monitoring and Data Collection

The National Institute of Allergy and Infectious Diseases, Vaccine Research Center, regulatory authority inspectors or their authorized representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial, provided that subject confidentiality is respected.

Clinical research data will be collected in a secure electronic data management system maintained by the VRC. Source documentation is entered into the subject's medical chart.

9.3 Policy Regarding Research-Related Injury

The study site will provide short-term medical care for any injury resulting from participation in this protocol. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the study sites, the National Institutes of Health, or the United States Federal Government.

9.4 Multi-site Management

The Vaccine Research Center, NIAID, NIH is the coordinating center as well as a site for this protocol. Each site that will be participating will have a site Principal Investigator and Associate Investigators (see Appendix II) who have parallel roles at their respective institutions in managing the conduct of the study at their sites in compliance with all applicable regulations and good clinical practices. The protocol plan is to establish a Reliance Agreement with each collaborating study site such that the NIAID IRB is the IRB of Record for the conduct of the protocol. If a reliance agreement is not established, the site will be required to obtain a local IRB review.

9.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

9.6 Publications Resulting from this Protocol

The specimens collected through this research protocol have been used in the support of assay development and validation which does not typically result in a publication of results, as well as laboratory research studies that have been published [7-24].

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APPENDIX I: INFORMED CONSENT FORM

The template informed consent forms are provided to guide development of a site-specific consent form. Only IRB-approved consent forms will be used to consent subjects for study participation.

Title: VRC 200: A Multicenter Specimen Collection Protocol to Obtain Human Biological Samples for Research Studies

VRC 200 Standard Informed Consent Form Template

INTRODUCTION

We invite you to take part in a research study at the [insert name of institution].

First, we want you to know that:

> Taking part in [insert name of institution] research is entirely voluntary.
>
> You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the [insert name of institution], you must be taking part in a study or be under evaluation for study participation.
>
> You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your [insert name of institution] doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at [insert name of institution], or with family, friends or your personal physician or other health professional.

PURPOSE AND PROCEDURES

The purpose of this study is to collect biological specimens for research purposes. Parts of the blood are often needed in research studies. Other types of specimens sometimes needed for research are other blood components, body fluids (such as semen or urine), or secretions (for example, from the nose, mouth, or different skin areas). A skin sample (biopsy) is another type of specimen that is sometimes useful for research.

Scientists at the Vaccine Research Center (VRC) will use these samples for research studies of different diseases and immune system responses, including HIV, hepatitis, responses to infections, vaccinations and other medical research. Even if you do not have a disease, your samples can be used to try to discover ways to prevent or treat medical conditions. Standard approved medical procedures will be used to collect these samples.

The following must be true for you to be eligible for the study:

- You must be age 18 years or older
- You must be able and willing to complete the informed consent process
- You must be willing to provide samples that will be stored for future research

- You must be able to provide proof of your identity

You must sign this consent before we can begin screening. Signing this form indicates that you are willing to be screened and, if eligible, you may enroll. If the screening shows that you are not eligible for the study, you will not be enrolled. A doctor or nurse will ask you some questions about your medical history and perform a physical exam.

You have the right to refuse any of the types of samples collections procedures at any time. You may not be offered certain types of sample collections if there is not a need for such samples by any research laboratories at the time of your visit. You may not be eligible for some types of sample collections. A study nurse or physician will check for your eligibility for the sample collections that have special requirements.

Your consent to enroll will be consent to collect samples for up to a one-year period. After that, if more samples are needed and you wish to continue participating in this protocol, you must sign a new consent form each year.

As many as 3,000 people may participate in this study. The actual number may be lower or be higher, depending on the need for research samples and the willingness of subjects to participate. Most subjects will have only one or a few samples collected. Different types of samples are discussed in the consent, but only certain types of sample types may be collected from you. This will be discussed in advance before the sample is collected.

BLOOD SAMPLES

Blood will be drawn by standard phlebotomy techniques from veins in the arms or hands only. Typically, about 100 mL (about 6 tablespoons) of blood will be drawn from your arm for testing. More or less may be drawn depending upon the research needs. The study staff will discuss the blood draw plan with you before starting.

URINE, SEMEN, SALIVA OR SWAB SAMPLES

If applicable and needed, samples of urine, semen, or saliva may also be collected for research use.

For urine and semen samples, you will collect the sample in private by yourself with a cup.

Some samples will be collected by a swab, a nurse or doctor will use a swab (like a Q-tip) to brush a part of your body, such as over a skin area or inside the nose, the mouth, vagina, or penis. For certain types of swab samples, for example around the anal area, you may collect the sample yourself, in private.

SKIN BIOPSY

If you are willing and eligible, and a skin sample is needed for research, then a separate consent will be signed, which explains the procedure and risks.

APHERESIS

We may ask you to provide blood samples collected by a procedure called “apheresis.” To be eligible for apheresis:

- You must not have an unstable heart as indicated by your medical history and test results
- You must not have blood pressure greater than 180/100
- You must not have a known blood clotting disorder

- You must not be breast feeding
- If you are a woman who could get pregnant, you will have a urine or blood pregnancy test within 72 hours before the apheresis procedure. The test must show that you are not pregnant
- You must not to have a condition that the attending physician or the apheresis clinic staff considers a reason to not do an apheresis procedure

Before an apheresis is done, your weight, pulse and blood pressure will be checked, and you will have a blood test to be sure you are healthy enough to donate blood cells. You will be asked questions about your general health and medical history. You will be asked to lie on a recliner or couch.

The procedure is done using one needle placed into each arm. The kits used to collect the apheresis products are sterilized, single-use, disposable sets that are not in contact with any person's body fluids other than yours. No blood products are given to you during these procedures.

In the apheresis procedure, blood is removed through a needle in the vein of one arm, spun in a machine that permits separation of the desired blood component (white blood cells or plasma), and then the remainder is returned through a needle in the other arm. Citrate, a medication to prevent blood from clotting, is added to the blood while in the machine to prevent it from clotting.

The purpose of this procedure is to allow the investigator to obtain and study a larger number of white blood cells or plasma than would otherwise be possible by simple blood drawing. The number of white blood cells or plasma collected is a small fraction of the total amount in your body. The body quickly replaces removed cells and plasma. Similar procedures are used on a daily basis in the Blood Bank of the [insert name of institution] and by other blood banks as a means of obtaining blood products from normal donors and as a form of therapy for certain diseases. Your samples will not be used for transfusion or therapy, however. The procedure will take approximately 1-3 hours.

HEPATITIS SCREENING

Some of the blood drawn from you as part of this study may be used to screen for different types of viral liver infections, such as hepatitis. If the tests show evidence of hepatitis or other medical conditions, you will be informed of the results. If you do not have a regular physician, the study team will assist in referring you to an appropriate physician for evaluation.

GENETIC TESTING

Some of the blood drawn from you as part of this study will be used for genetic tests. Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Your blood sample used in these genetic tests will not have your name on it, and the results will not be in your medical record. These tests are not used to check your health, and we will not tell you the results.

NIH Site only: A special genetic test, called HLA typing, may be done by the NIH Clinical Center medical laboratory. These results will be in your medical record, but they will not be used to check your health. Any genetic testing, including HLA typing, is for research purposes only. Any genetic information collected or learned about you will be kept confidential. Medical

records, including HLA test results, are kept securely. We will not give any genetic information that is in your medical record to anyone without your permission.

If HLA typing is done in a research laboratory, the result will not be included in your medical record.

HIV TESTING

As part of this study, we will test you for infection with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. If you are infected with HIV, you will still be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

STORED SAMPLES

To be eligible for the study, you must also be willing to allow some of your blood and other samples to be stored for future research on HIV disease, the immune system, or other medical conditions.

Generally, the results from the research done with your stored samples will not be given to your private doctor and will not be put in your medical record. This is because the test results, unlike routine medical testing, may be experimental or preliminary. The relevance of these tests to your care may be unknown. However, at your request, the results of any research tests will be discussed with you or your physician by one of the investigators.

Labeling of stored samples: Your stored samples will be labeled with a code (such as a number) that only the study team can link to you. Any identifying information about you will be kept confidential to the extent permitted by law.

Future studies: Your samples may be kept in storage for a long time and used in the future by medical researchers. When the study team shares your samples, they will share it with only a code on it. Some information about you, such as your gender, age, health history, or ethnicity may also be shared with other investigators.

Your stored materials will be used only for research and will not be sold or used for treating other people. The research done with your materials may be used to develop new products in the future, but you will not receive payment for such products.

RISKS

Blood drawing may cause pain, bruising, and, rarely, infection at the site where the blood is taken.

Collection of samples by swabs rubbing over the inside of the nose, inside the mouth, vagina, penis or skin can cause temporary discomfort.

Apheresis Procedure Risks: Apheresis donations are generally safe and side effects are rare. Pain, bruising or discomfort at the needle placement site may occur. Sometimes apheresis causes a tingling sensation around the mouth or in the finger, chills, nausea, heartburn or mild muscle cramps. This can usually be relieved by slowing or temporarily interrupting the apheresis or taking a calcium containing antacid, such as Tums®. Other possible side effects are anxiety, vomiting, and lightheadedness. Temporary lowering of the blood pressure may develop. There is the rare possibility of infection, fainting or seizure. There may also be a slightly increased

bleeding tendency for a few hours after the procedure due to the temporary presence of the anticoagulant. Very rarely a nerve problem at the needle placement site may occur. There are theoretical risks from re-infusion of the blood after processing by the machine such as infection or an adverse reaction to the blood components. However, these risks must be exceedingly rare if they occur, since they have not been seen in many thousands of subjects who have undergone this or similar procedures to date. Rarely the performance of frequent apheresis procedures over a short period of time can result in a drop in total blood cell counts, including the absolute CD4+ T cell count (a type of blood cell that fights infection), or a drop in the platelet count (a type of blood cell that helps blood to clot). The extent or duration of the drop in these cell counts may be unpredictable and vary from person to person. The short or long-term risks associated with these drops are also unknown, and they could possibly be more serious in those individuals whose blood counts are already below the normal range as a result of HIV-1 infection or other medical conditions.

Based upon your blood cell counts or other medical conditions, we may limit the number of times that you are eligible to undergo apheresis over a set period of time. Blood cell counts and other safety blood studies may be checked periodically during the time that you are enrolled on this protocol. You will be informed about the results of the type of routine blood tests that are done to check on the state of your health. There may be additional risks of apheresis that are unknown at this time. Any new information that may affect your willingness to participate in this study will be disclosed to you.

BENEFITS

There will be no direct benefit to you for participating in this protocol. The knowledge gained through this research may benefit others in the future.

UNKNOWN RISKS or BENEFITS

Some routine medical tests may be performed during study participation. You may learn new information about your health. Receiving a new diagnosis may be stressful. You may feel that learning new information about your health is a benefit of study participation. Or you may feel this is risk of study participation.

ALTERNATIVES

This study procedures are not being done to treat a medical condition. You may choose to not participate in any or all of the procedures discussed.

COMPENSATION

[Site specific information]

You will be compensated [insert amount] for each visit than includes an apheresis procedure, [insert amount] for each visit (without apheresis) that includes procedures that require a needle-stick, and [insert amount] for clinic visits in which there is no needle-stick. If a skin biopsy is performed, extra compensation is provided and this is discussed in the skin biopsy consent.

Compensation will be provided [add site-specific time for when compensation will be provided].

Total compensation is based on the number of study clinic visits and the type of sample collection performed. Your compensation may need to be reported to the Internal Revenue Service (IRS) as taxable income.

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study without your consent for the following reasons:

- The NIH doctor feels that staying in the study is harmful to you.
- The study is cancelled or stopped.
- You don't keep appointments or follow study procedures.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for any of the costs that are directly related to this study. However, the costs of any other medical care you may need during this period will be your responsibility.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the [insert name of institution] will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the [insert name of institution] will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your [insert name of institution] medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The [insert name of institution] will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, [insert name of institution] or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the [insert name of institution] policies. In general, patients are not paid for taking part in research studies at the [insert name of institution]. Reimbursement of travel and subsistence will be offered consistent with [insert name of institution] guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the principal investigator, [insert name] at [insert number], or Study Coordinator, [insert name] at [insert phone number]. You may also call the Clinical Center Patient Representative at

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative	Date	Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM [insert date] THROUGH [insert date].

Signature of Investigator	Date	Signature of Witness	Date
Print Name		Print Name	

APPENDIX II: CONTACT INFORMATION

Study Chair and VRC Site Principal Investigator / VRC Associate Investigators / Study Coordinators / Study Site / Data Coordinating Center	Scientific Collaborators / Laboratory / Apheresis Clinic / Protocol Operations
Study Chair and VRC Site Principal Investigator: Grace Chen, M.D., M.P.H. Vaccine Research Center, NIAID, NIH 40 Convent Drive Bethesda, MD 20892 **VRC Associate Investigators**: Barney Graham, M.D., Ph.D., 301-594-8468 Joseph Casazza, M.D., Cynthia Starr Hendel, CRNP Lasonji Holman, FNP Sarah Plummer, RN, MSN, NP 301-402-8640 Martin Gaudinski, M.D., Abidemi .O. Ola, MSN, FNP., 301-761-7641 Cristina A. Carter, M.D., Allison Beck, PA-C, MPAS, Alicia Widge, M.D., M.S., **VRC Study Coordinators / Research Nurses:** Ingelise Gordon, RN, Study Coordinator All Clinic Staff: Pamela Costner, RN, BSN Jennifer Cunningham, RN, BSN Brenda Larkin, RN, BSN, MBA Floreliz Mendoza, RN Laura Novik, RN, BSN, MA Jamie Saunders, RN, BSN William Whalen, RN, BSN Xioalin Wang, RN, BSN Aba Mensima Eshun, RN, BSN Anita Arthur, RN, BSN **VRC Study Site**: National Institutes of Health Clinical Center 5NES Vaccine Evaluation Clinic Bethesda, MD 20892 **Data Coordinating Center** EMMES Corporation: Rockville, MD 20850	**Scientific Collaborators**: Robert Bailer, Ph.D., Daniel Douek, M.D, Ph.D., Richard Koup, M.D., Peter Kwong, Ph.D., John Mascola, M.D., Mario Roederer, Ph.D., Richard Schwartz, Ph.D., Robert Seder, M.D., Nancy Sullivan, Ph.D., Emily Coates, Ph.D., Josephine Cox, PhD., Katherine Houser, PhD., Adrian McDermott, Ph.D., Eli Boritz, M.D., Ph.D., Julie Ledgerwood, D.O., **Research Immunology Central Laboratory:** VITL (Vaccine Immunology Testing Laboratory) 9 West Watkins Mill Road, Suite 150 Gaithersburg, MD 20878 **NIH Apheresis Clinic** Kamille A. West, MD Chief, Blood Services Section Department of Transfusion Medicine NIH Clinical Center Bldg 10 Room 1C711E Bethesda, MD 20892 Phone: kamille.west@nih.gov **VRC Protocol Operations:** Maria C. Burgos Florez, M.Sc., Galina Yamshchikov, M.S., Nina M. Berkowitz, M.P.H., Olga Vasilenko, M.S., Iris Pittman, BA, CCRP, Ro Shauna S. Rothwell, Ph.D., 301-761-746 Lam Ngan Le, MBA, CCRP., Somia Hickman, Ph.D., Eugeania Burch, M.P.H., Olga Trofymenko, MD.,

VRC Recruitment Team: / Preeti Apte, MHA, BA Cora Trelles Cartagena, BSW Renunda Hicks	

Collaborating Sites	Site Investigators of Record
Site: The University of Puerto Rico - Medical Science Campus (UPR MSC) Puerto Rico Clinical and Translational Research Consortium (PRCTRC)	
Clinic Location:	1st Floor University Hospital San Juan, Puerto Rico 00936-5067
Principal Investigator:	Clemente Diaz, M.D., 1st Floor University Hospital P.O. Box 365067 San Juan, Puerto Rico 00936-5067 clemente.diaz@upr.edu
Associate Investigators:	Irma Febo, MD
Study Coordinators:	Aileen Rivera Maldonado, RN, MSN Carmen M Rivera Torres, RN, MPH Lizzie Ramos Tolinchi, MPH
Research Nurses:	Barbara Guzmán, RN, MPH Sheyla Garced, RN, MS

Contact information for collaborations added after VRC 200, Version 1.0 approval:

Contact	Research Collaboration
Antonio Lanzavecchia, M.D. Institute for Research in Biomedicine Via Vincenzo Vela 6 CH-6500 Bellinzona Switzerland 41-91-8200310 lanzavecchia@irb.unisi.ch	Approved as Amendment L (OPS approval 4/11/07) The VRC will send stored specimens to a non-NIH collaborator for laboratory research related to immune responses to antigens associated with filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g. Lassa fever virus). This immunological research will include isolation of human monoclonal antibodies. The laboratory data will then be provided to VRC in support of VRC vaccine research. Hybridomas secreting the monoclonal antibodies identified through this collaboration will also be provided back to VRC as part of this collaboration.
Georgia Tomaras, Ph.D. Duke Human Vaccine Institute 106 Research Drive MSRB II, 4th Floor Duke University Medical Center 103020 Durham, NC 27710 gdt@duke.edu	Approved as Version 6.0, Letter of Amendment #1 (OPS Amendment P approval 1/17/08) Coded blood samples, without personal identifying information, will be sent to the Duke Human Vaccine Institute for the conduct of *in vitro* assays that are based on previously published methods and evaluate for the viral suppression activity of activated T cells. The VRC will collaborate with this research group to use these data, as well as other measures of immunogenicity, towards the goal of better understanding of immune responses to vaccines and viral pathogens.
Rafik Sekaly, M.D. Université de Montréal, CR-CHUM Institut National de la Santé et de la Recherche Médical, U743 Montréal, Québec, H2X1P1 Canada rafick-pierre.sekaly@umontreal.ca x0728	Approved as Version 6.0, Letter of Amendment #2 (OPS Amendment R approval 2/29/08) Coded peripheral mononuclear blood cell samples, without personal identifying information, will be sent to Montreal University to perform *in vitro* gene array assays towards the goal of better understanding host genetic factors that affect immune responses.
Jacob D. Estes, Ph.D. The AIDS and Cancer Virus Program SAIC-Frederick, Inc. NCI-Frederick Fort Detrick Campus Bldg. 535, Rm. 413b Frederick, MD 21702 estesj@mail.nih.gov	New in Version 7.0 Coded skin biopsy samples may be sent to the AIDS and Cancer Virus program for immunohistochemistry; evaluations may include assessments for neutrophils, B cells, T lymphocytes [including retinoid-related orphan receptor gamma t (RORgt) and interleukin 17 to assess for Th17 cells], defensins and other immunohistochemistry parameters. Microarrays may be performed on the tissue, and if sufficient quantity is available, flow cytometry to look at T cell subsets and cytokine expression.
Clemencia Pinilla, Ph.D. Torrey Pines Institute for Molecular Studies 3550 General Atomics Court San Diego, CA 92121	Approved as Version 7.0, Letter of Amendment #1 (OPS Amendment X approval 9/9/08) Coded PBMC samples, without personal identifying information, will be sent to the Torrey Pines Institute for

cpinilla@tpims.org	Molecular Studies to identify new epitopes within vaccinia. These epitopes may be relevant vaccine targets and they will make possible new analyses of immune responses in vaccine evaluation and studies of disease pathogenesis.
Stephen De Rosa, Ph.D. HVTN Laboratory Program Fred Hutchinson Cancer Res Ctr 1100 Fairview Ave. North, LE-200 Seattle, WA 98109-1024 Phone: Fax: Email: sderosa@fhcrc.org Guido Ferrari, M.D. CHAVI Duke Repository Assistant Research Professor Department of Surgery Duke University Medical Center DUMC Box 2926 Durham, NC 27710 Phone: Fax: Email: gflmp@duke.edu Jill Gilmour, Ph.D. Senior Director, Clinical Research IAVI Core Laboratory 5th floor, St. Stephens Centre Chelsea and Westminster Hosp. 369 Fulham Road London, SW 10 England 9NH Phone: Email: jgilmour@iavi.org	Approved as Version 7.0, Letter of Amendment #2 (OPS Amendment Z approval 12/17/08) Coded blood samples, without personal identifying information, will be sent to the three research laboratories listed for work on the development of immunological assays, including virus suppression assays and a new intracellular cytokine staining method.
Terence M. Tumpey, Ph.D. Centers for Disease Control and Prevention Influenza Division, Mail Stop G-16 1600 Clifton Road N.E. Atlanta, GA 30333 Phone: Fax:	Approved as Version 8, Letter of Amendment #1 (OPS Amendment CC approval 5/20/09) Coded blood samples, without personal identifying information, will be sent to Dr. Tumpey for work on the assessment of influenza immune responses.
HVTN Laboratory Program University of Washington Virology Specialty Laboratory Seattle, WA	New in Version 9.0; updated in Version 10, Letter of Amendment#2 (OPS LL approval 6/18/13) Coded blood samples, without personal identifying information, from prior HVTN study participants who need long-term follow-up HIV testing will be sent to the HVTN Laboratory. This laboratory may also collaborate on a variety of virologic assays using coded samples from VRC 200 subjects (whether or not a prior HVTN study participant).
James Crowe, M.D. Vanderbilt University, Pediatrics and Infectious Disease 1161 21st Ave South D-7240 MCN	Approved as Version 9, Letter of Amendment #1 (OPS Amendment II approval 11/29/10)

Nashville, TN 37232-2581 Phone: Email: james.crowe@vanderbilt.edu	Coded blood samples, without personal identifying information will be sent for laboratory research related to immune responses to antigens associated with filoviruses (e.g., Ebola, Marburg) and other pathogens. This immunological research will include isolation of human monoclonal antibodies. The laboratory data will then be provided to VRC in support of VRC vaccine research. Hybridomas secreting the monoclonal antibodies identified through this collaboration will also be provided back to VRC as part of this collaboration.
Joseph J. Mattapallil, D.V.M., Ph.D. Dept. of Microbiol. & Immunology F. Edward Herbert Schl. of Med. Uniformed Services University 4301 Jones Bridge Road Bethesda, MD 20814 Telephone: e-mail: joseph.mattapallil@usuhs.edu	Approved as Version 10, Letter of Amendment #1 (OPS Amendment KK. approval 4/30/12) Coded stored specimens will be provided for laboratory research related to regulation of immune responses in HIV-infected subjects. Non-identifying demographic data and antiretroviral therapy (ART) status may be provided to facilitate the analysis. The laboratory data will also be provided back to VRC as part of this collaboration.
Jason Brenchley, Ph.D. Senior Investigator NIAID, Viral Pathogenesis and Vaccine Section Laboratory of Molecular Microbiology 4 Center Drive, Room 201 Bethesda, MD 20892-0460 Phone: Email: jbrenchl@niaid.nih.gov	Approved as Version 10, Letter of Amendment #3 (OPS Amendment MM. approval 7/31/13) The VRC will send coded blood/PBMC specimens to this NIH collaborator for laboratory research related to the level of transcription factors known to be important for CD4/CD8 differentiation in sorted subsets of PBMC. Non-identifying demographic data may be provided to facilitate the data analysis.
Cristine Kinross, Ph.D. Sr. Product Manager Epicentre, an Illumina company 5602 Research Park Blvd, Suite 200 Madison, WI 53719 Phone: Email: Cristine.Kinross@epicentre.com	New in Version 11.0 The VRC will send coded specimens which will be used to sequence all HIV transcript molecules derived from cellular samples of a group of HIV-infected donors using the Illumina next generation deep sequencing platform. Epicentre's novel technology specifically removes host cell-associated transcripts from total RNA specimens, leaving only pathogen-derived material for deep sequencing. This technology will allow characterization of HIV gene expression in individual samples and comparison across samples to reveal any variation in the way the virus expresses its genes in different cells types, and in different donors.
Mary N. Carrington, Ph.D. Laboratory of Experimental Immunology Head, HLA Typing Section Center for Cancer Research National Cancer Institute Building 560, Room 21-89 Frederick, MD 21702-1201	Approved as Version 11, Letter of Amendment #1 (OPS Amendment OO. approval 2/20/14) The VRC will send coded specimens for HLA type and related immunological assessments. Non-identifying demographic data may be provided to facilitate the data analysis.

Ted C. Pierson, Ph.D. Senior Investigator Chief, Viral Pathogenesis Section Laboratory of Viral Diseases, NIAID, NIH 33 North Drive Building 33, Room 2E19A.2 Bethesda, MD 20892	New in Version 12.0 The VRC will send coded specimens for neutralization assay and related immunological assessments. Non-identifying demographic data may be provided to facilitate the data analysis.
Chih-Jen Wei, Ph.D. Director, Synthetic & Immune Biology Bio-Innovation, Global Bio-Therapeutics Sanofi US 270 Albany Street Cambridge, MA 02139 Tel.: Cell: Email: chih-jen.wei@sanofi.com	Approved as Version 14.0, Letter of Amendment #1 (OPS Amendment TT. Approval 03/9/2016) The VRC will send coded blood/serum specimens to the scientific collaborator for research related to the development of a Zika virus vaccine. Non-identifying demographic data may be provided to facilitate the data analysis.
Sujatha Rashid, MS, PhD, PMP Senior Scientist, Virology BEI Resources www.beiresources.org 10801 University Boulevard Manassas, VA 20110-2209 Tel: ext. 2660 Email: srashid@atcc.org	Approved as Version 14.0, Letter of Amendment #2 (OPS Amendment UU. Approval 03/23/2016) As requested by DMID/NIAID, the VRC will send coded blood/serum specimens to the BEI repository (https://www.beiresources.org/) and the contact person there to receive the samples is noted below. The samples will be used for Zika virus related research. Only non-identifying demographic data may be provided to facilitate the data analysis.
Joseph Campo, Ph.D. Antigen Discovery, Inc. 1 Technology Drive, STE E 309 Irvine, CA 92618 Tel: David M. Koelle, M.D. University of Washington School of Medicine 750 Republican St, Room E651 Seattle, WA 98109 Tel:	Approved as Version 14.0, Letter of Amendment #3 (OPS Amendment VV. Approval 05/11/2016) The VRC will send coded PBMCs specimens to Antigen Discovery, Inc. and University of Washington, the contact persons there to receive the samples are noted below. The samples will be used to isolate Pf-specific T cell responses and characterize antigen specificity. Only non-identifying demographic data may be provided to facilitate the data analysis.

Dan Barouch, MD, PhD Beth Israel Deaconess Medical Center E/CLS-1047 330 Brookline Ave Boston, MA 02215 Tel: Fax: Email: dbarouch@bidmc.harvard.edu Stephen S. Whitehead, PhD Laboratory of Infectious Diseases, NIAID, NIH Bldg 33, Room 3W10A 33 North Drive, MSC 3203 Bethesda, MD 20892-3203 Telephone: Fax: Email: whitehead@niaid.nih.gov	Version 14.0, Letter of Amendment #4 The VRC will send coded blood/serum specimens to the scientific collaborators for research related to the development of a Zika virus vaccine. Only non-identifying demographic data may be provided to facilitate the data analysis.
Mark Page, PhD Division of Virology National Institute for Biological Standards and Control (NIBSC) Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG UK Tel: 01707 641 283 Email: mark.page@nibsc.org	As part of the global initiative for assay standardization, NIBSC in conjunction with its partners (such as National Control Laboratories and WHO Collaborating Centers) will collect and analyze Zika antibody positive serum and plasma in an international collaborative study. All study data will be anonymized and statistically analyzed by NIBSC in accordance with the WHO guidelines on biological standardization. A formal report will be submitted to the WHO Expert Committee for Biological Standardization for endorsement as an International Standard.
Matthew Bonaparte, Ph.D. Sanofi Pasteur Deputy Director Project Representation Global Clinical Immunology 1 Discovery Drive Swiftwater, PA 18370 Telephone: Email: Matthew.Bonaparte@sanofipasteur.com	These serum samples will be used for development of research level serological assays to assess immune response to Zika vaccination and/or infection, and evaluation of assay specificity in the case that prior exposure to Dengue virus can be demonstrated.
Jonathan F. Smith, Ph.D. Chief Scientific Officer PaxVax 3985-A Sorrento Valley Blvd San Diego, CA 92121 Telephone: Email: jsmith@paxvax.com	The VRC will send coded blood/serum specimens to the scientific collaborator for passive transfer protection studies in non-human primates, and for the assessment of vaccine - induced immune response.

Alessandro Sette, Dr. Biol. Sci. Center Head, Division Head, and Professor Center for Infectious Disease, Division of Vaccine Discovery La Jolla Institute for Allergy and Immunology 9420 Athena Circle La Jolla, California USA Telephone: Email: alex@lji.org	The VRC will send coded blood samples to the scientific collaborator at the La Jolla institute. These samples will be used to characterize T-cell reactivity and the immune response to Zika. Only non-identifying demographic data may be provided to facilitate the data analysis.
James Rogers, PhD Manager Battelle Biomedical Research Center www.battelle.org 1425 Plain City-Georgesville Rd (St Rt 142) West Jefferson, OH 43162 Telephone: Email: rogersjv@battelle.org	The VRC will send coded blood/serum specimens to Battelle. The samples will be used for Zika virus related research and assay development. Only non-identifying demographic data may be provided to facilitate the data analysis.
David I Watkins, Ph.D. Professor of Pathology Vice-Chair Research Dept. Pathology University of Miami Leonard M. Miller School of Medicine Life Sciences Technology Park 1951 NW 7th Avenue, Suite 2340 Miami, FL 33136 Telephone: Cell: E-mail: dwatkins@med.miami.edu	The VRC will send coded serum and/or plasma samples to the scientific collaborator at the University of Miami Leonard M. Miller School of Medicine. The serum and/or plasma samples will be used for development of serological assays to assess immune response to Zika infection and/or vaccination.
Kayvon Modjarrad, M.D., Ph.D. Associate Director, Emerging Infectious Disease Threats Military HIV Research Program / Walter Reed Army Institute of Research 6720A Rockledge Drive, Suite 400, Bethesda, MD 20817 USA Telephone: Cell: Email: kmodjarrad@hivresearch.org	The VRC will send coded serum or plasma samples to the scientific collaborator at the Walter Reed Army Institute of Research. The serum or plasma samples will be used for the evaluation of Zika immune responses.

Marc Fischer, MD, MPH Arboviral Diseases Branch Centers for Disease Control and Prevention mfischer@cdc.gov	The VRC will send coded serum and/or plasma samples to the scientific collaborator at the Centers for Disease Control and Prevention. The serum and/or plasma samples will be used for development of serological assays to assess immune response to Zika infection and/or vaccination.
Manoj K. Pastey DVM, MS, PhD Associate Professor Head, Molecular Diagnostic Laboratory 105 Magruder Hall College of Veterinary Medicine Oregon State University Corvallis, OR 97331 Telephone: Email: Manoj.Pastey@oregonstate.edu	The VRC will send coded samples to the scientific collaborator at OSU. The samples from HIV infected individuals will be used to identify antibodies against HIV NS2 protein by ELISA assay.
Hansi Dean, PhD Vice President and Head Discovery Research Takeda Pharmaceuticals 40 Landsdowne Street Office: 75 Sidney-3062 Cambridge, MA 02139 Telephone: Email: hansi.dean@takeda.com	The VRC will send coded serum and/or plasma samples to the scientific collaborator at Takeda Inc. The serum and/or plasma samples will be used for development of serological assays such as ELISA and neutralizing antibody assays.
Anuja Matthew, PhD, M.Sc. Research Associate Professor Institute for Immunology and Informatics University of Rhode Island 80 Washington St. Room 334B Providence, RI 02903 Tel: Email: mathewa@uri.edu	The VRC will send coded blood/PBMCs specimens to Anuja Mathew at the University of Rhode Island. The samples will be used to assess adaptive immunity to flaviviruses including ZIKV. Dr. Matthew and her group will assess B cell and antibody responses (in supernatants) and characterize Flavivirus specificity. Only non-identifying demographic data may be provided to facilitate the data analysis.
Gregory A. Poland, M.D., MACP, FIDSA, FRCP Director, Mayo Vaccine Research Group 611C Guggenheim Building Mayo Clinic and Foundation 200 First Street, SW Rochester, MN 55905 Tel: Email: poland.gregory@mayo.edu	The VRC will send coded blood/PBMCs specimens to the Mayo Vaccine Research Center. These samples will be used to characterize T-cell and immunologic responses to Zika. Only non-identifying demographic data may be provided to facilitate the data analysis.

Allison M.W. Malloy, MD, MSc Department of Pediatrics Infectious Disease Faculty F. Edward Hebert School of Medicine - "America's Medical School" Uniformed Services University of the Health Sciences (USU) 4301 Jones Bridge Road Rm A3028 Bethesda, Maryland, 20814 allison.malloy@usuhs.edu	The VRC will send coded blood specimens to Allison Malloy at the Uniformed Services University of the Health Sciences. These samples will be used for analysis of T cells and dendritic cells from healthy volunteers for response to natural influenza virus infection. Only non-identifying demographic data may be provided to facilitate the data analysis.
Andrew Ward, Ph.D. Department of Integrative Structural and Computational Biology The Scripps Research Institute 10550 North Torrey Pines Road, La Jolla, CA 92037 andrew@scripps.edu	The VRC will send coded serum samples to Andrew Ward at the Scripps Research Institute. These samples will be used to determine the epitopes on the HKU-1 coronavirus spike protein that are bound by polyclonal antibodies. Only non-identifying demographic data may be provided to facilitate the data analysis.
Surender Khurana, Ph.D. Div. of Viral Products Center for Biologics Evaluation and Research (CBER) US Food and Drug Administration (FDA) Bldg-52/72, Rm-1230 10903 New Hampshire Avenue Silver Spring, MD-20993 Surender.Khurana@fda.hhs.gov	The VRC will send coded serum samples to Surender Khurana at CBER. These samples will be used for antibody analysis. Only non-identifying demographic data may be provided to facilitate the data analysis.
Carl Hansen, Ph.D. Director & CEO AbCellera Biologics Inc. 2215 Yukon Street Vancouver, BC V5Y 0A1 carl.hansen@abcellera.com	The VRC will send coded blood samples to Carl Hansen at AbCellera. These samples will be used for antibody identification analysis. Only non-identifying demographic data may be provided to facilitate the data analysis.

APPENDIX III: TEMPLATE SKIN BIOPSY CONSENT

The sample informed consent forms are provided to guide development of a site-specific consent form. Only IRB-approved consent forms will be used to consent subjects for study participation.

Title: VRC 200: A Multicenter Specimen Collection Protocol to Obtain Human Biological Samples for Research Studies

Skin Biopsy Consent

INTRODUCTION

We invite you to take part in a research study at the [insert name of institution].

First, we want you to know that:

> Taking part in [insert name of institution] research is entirely voluntary.
>
> You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the [insert name of institution], you must be taking part in a study or be under evaluation for study participation.
>
> You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your [insert name of institution] doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at [insert name of institution], or with family, friends or your personal physician or other health professional.

PURPOSE OF THE STUDY

You are participating in a protocol for the donation of blood, tissue, or other samples for laboratory research. This consent is to offer you the choice of making a skin biopsy donation. Skin biopsy samples can be useful in laboratory research.

A skin biopsy is a medical procedure that removes a small piece of skin. A separate consent for the skin biopsy is needed for two reasons. First, you may choose not to have a skin biopsy. Second, you should understand the way a skin biopsy is done and the risks of a skin biopsy before deciding whether to have one.

If you have a skin biopsy, it will be done at the [insert name of institution]. You will also be treated there if any side effects of the skin biopsy occur.

You will be told of any new information learned during this study that might cause you to change your mind about having a skin biopsy. When a skin biopsy is collected for research in this study, it is usually not sent to the regular hospital lab for a "pathology" report. If it is sent to see if there are any abnormal medical conditions, then you will be told before it is sent and will be informed of the result. The report will be in your medical record. Samples given to research labs and results of any test performed will be labeled only with your study identification number. The results of any tests done by research laboratories with your skin sample will <u>not</u> be in your medical record.

STUDY PROCEDURES

A skin biopsy is done in an outpatient clinic. You will receive a medicine such as lidocaine with epinephrine to reduce pain and bleeding. Medicine to reduce pain is called an anesthetic. The anesthetic may be given by injection or applied to the skin at the place where the skin biopsy will

be done. The anesthetic may sting briefly. If you have ever had an allergic reaction to a numbing medicine, such as novocaine or lidocaine, which are commonly used by dentists or surgeons, do not sign this consent until the details of your allergic reaction have been discussed with a study doctor.

After the skin is numb, a sharp, hollow instrument will be used to remove a small, circular piece of skin. The circle will be about the size of a pencil eraser. This biopsy method is called a "punch biopsy." After the punch biopsy, the skin may be closed with one or two stitches. You must follow the directions given to you for keeping the area clean until it heals. You must return to the clinic for the appointment given to you to have the stitches removed several days later. Careful methods and clean equipment will be used to prevent infection.

If you are invited to have a skin biopsy for research because it is known to be an area being treated for a local infection, then photos may be taken. You must inform the clinic promptly if you have any fever, swelling, increased pain or increased area of infection.

RISKS OF SKIN BIOPSY

Any time the skin is opened there is a chance of infection. If there is a known infection at the biopsy site then healing may take longer. Infection after a skin biopsy is rare and care will be taken to try to prevent infection. You may have pain or discomfort during the skin biopsy or while it is healing. You may have a very small amount of bleeding right after the skin biopsy. You will have a small scar. If you have skin that tends to form large scars of the type called "keloids," then you will have risk of a keloid forming at the biopsy area. A history of keloid formation increases the risk for keloid scarring from the skin biopsy. If you have a known history of keloid scarring you are advised to inform the study staff and not have a skin biopsy that is only for research purposes.

Rarely, the anesthetic medicine used to numb the skin may cause an allergic reaction. In rare cases allergic reactions to medications can be life threatening. In rare cases anesthetic medications can cause an abnormal heart rhythm. The anesthetic may also interact with certain other medicines to cause serious side effects. Be sure to review all your medications and drug use with the study staff before agreeing to have a local anesthetic. Certain antidepressant medicines and illicit drugs such as cocaine are among the drugs that can react with anesthetics to cause side effects.

BENEFITS

You may have no benefit from the skin biopsy. If your skin has a medical condition you may learn more about the cause of the problem.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for the skin biopsy or care of the skin biopsy. However, the costs of any other medical care during the period will be charged to you or your insurance company.

PAYMENT TO YOU FOR YOUR PARTICIPATION

[Site specific information]

You will be paid [insert amount] above the usual compensation for a visit that includes a skin biopsy. The skin biopsy stitches will be removed about 7-10 days later.

Compensation will be provided [add site-specific time for when compensation will be provided].

Total compensation is based on the number of study clinic visits and the type of sample collection performed. Your compensation may need to be reported to the Internal Revenue Service (IRS) as taxable income.

ALTERNATIVES

You may choose to not have a skin biopsy.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the [insert name of institution] will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the [insert name of institution] will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your [insert name of institution] medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The [insert name of institution] will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, [insert name of institution], or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the [insert name of institution] policies. In general, patients are not paid for taking part in research studies at the [insert name of institution]. Reimbursement of travel and subsistence will be offered consistent with [insert name of institution] guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, [insert name], at [insert phone number], or Study Coordinator [insert name] at [insert phone number].

You may also call the Clinical Center Patient Representative at

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative ______ Date ______ Print Name ______

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM [insert date] THROUGH [insert date].

Signature of Investigator ______ Date ______ Signature of Witness ______ Date ______

Print Name ______ Print Name ______

APPENDIX IV: REMOTE SAMPLE COLLECTION PROCEDURES

Procedures for Obtaining Informed Consent Over the Telephone and Conducting a Remote Enrollment into VRC 200 (03-I-0263)

Obtaining consent by telephone may be used for this protocol when a subject with unusual or difficult to find characteristics that are key to research being conducted does not reside locally and is willing to have a medical care provider collect research blood samples for shipment to the VRC.

The process for obtaining consent by telephone is as follows:

- The Clinical Staff will provide forms needed for the offsite admissions process, if needed, and a current copy of the protocol consent document for remote enrollments. The Clinical Staff will also provide appropriate return-addressed shipper(s) for returning the admissions forms, signed consent document and samples collected.
- After allowing time for receipt and review of the consent document, a Clinical Staff member who is authorized to obtain consent for the protocol will contact the subject by telephone at a mutually agreeable time to discuss the consent in the presence of a witness who is with the subject.
- The Clinical Staff will ask the subject to verify his/her identity by stating their first and last name, and date of birth.
- Once verification is determined, the Clinical Staff will review the elements of the consent with the subject.
- The Clinical Staff will allow the subject to verbalize any questions or concerns and will answer all questions to the satisfaction of the subject.
- If the subject agrees to consent, the Clinical Staff will inform the subject that he/she will be placed on a speakerphone so that the audible consent can be witnessed by a witness present with the staff member.
- Each witness will state his/her name. Each witness must be an adult. The witness present in the room with the Clinical Staff member will be another Clinical Trials Core staff member.
- For the witnesses, the subject will repeat his/her own first and last name, date of birth, and read the protocol name and number from the consent document.
- The subject will sign, date and time his/her copy of the consent document. The witness with the subject will also sign and date the consent document.
- The manner of obtaining consent, date, time and the names of the person administering the consent, providing consent and the name of the witness will be documented in the research record.
- Once the consent document is received by the site and checked for accuracy, it will be signed and dated with the day the consent process was conducted; typically this will be a date prior to when the original is received. The date the original is received by the site will be documented in the research record. The original document will be filed in the

medical record and a copy of the signed consent document will be mailed back to the subject.

The procedure for assignment of a study identification number, sample processing, and sample use is as follows:

The enrollment in the study database may be completed after the offsite admissions is completed and the telephone portion of the consenting is done and the subject and witness have verified verbally that the consent document is signed. Similarly, the blood samples may be collected by a qualified medical care provider that is with the subject after the telephone portion of the consenting is done. The offsite admissions form, consent document and sample may be sent in the same shipper or separate shippers as convenient to the persons involved. Before being sent to a research laboratory for processing, any label with a subject name or personal identifier will be removed and replaced with a label using the study identification number. The blood sample may be processed for proper storage upon arrival; however, it may not be used for research purposes until the signed consent document is received by the site.

INFORMED CONSENT FORM FOR REMOTE SAMPLE COLLECTION

The template informed consent forms are provided to guide development of a site-specific consent form. Only IRB-approved consent forms will be used to consent subjects for study participation.

Title: VRC 200: A Multicenter Specimen Collection Protocol to Obtain Human Biological Samples for Research Studies

VRC 200 Standard, for Consent by Telephone

INTRODUCTION

We invite you to take part in a research study at the [insert name of institution].

First, we want you to know that:

> Taking part in [insert name of institution] research is entirely voluntary.
>
> You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the [insert name of institution], you must be taking part in a study or be under evaluation for study participation.
>
> You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your [insert name of institution] doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at [insert name of institution], or with family, friends or your personal physician or other health professional.

PURPOSE AND PROCEDURES

The purpose of this study is to collect biological specimens for research purposes. Parts of the blood are often needed in research studies. Other types of specimens sometimes needed for research are other blood components, body fluids (such as semen or urine), or secretions (for example, from the nose, mouth, vagina, penis or different skin areas). A skin sample (biopsy) is another type of specimen that is sometimes useful for research. .

Scientists at the Vaccine Research Center will use the samples collected for research studies of different diseases and immune system responses, including HIV, hepatitis, responses to infections, vaccinations and other medical research. Even if you do not have a disease, your samples can be used to try to discover ways to prevent or treat medical conditions. Standard approved medical procedures will be used to collect these samples.

The following must be true for you to be eligible for the study:

- You must be age 18 years or older
- You must be able and willing to complete the informed consent process
- You must be willing to provide samples that will be stored for future research
- You must be able to provide proof of your identity

You must sign this consent before a research sample can be collected. This consent is for participants who are enrolling in the study through a consent process done over the telephone or

if already enrolled, having a sample collected remotely for shipment to the Vaccine Research Center at the NIH. The blood sample will be collected by a local medical care provider for this shipment.

Your consent to enroll will be consent to collect samples for up to a one-year period. After that, if more samples are needed and you wish to continue participating in this protocol, you must sign a new consent form each year.

As many as 3,000 people may participate in this study. The actual number may be lower or be higher, depending on the need for research samples and the willingness of subjects to participate. Most subjects will have only one or a few samples collected.

BLOOD SAMPLES

Blood will be drawn by standard phlebotomy techniques from veins in the arms only. Typically, about 100 mL (about 6 tablespoons) of blood will be drawn from your arm for testing. More or less may be drawn depending upon the research needs. The study staff will discuss the blood draw plan with you before starting.

HEPATITIS SCREENING

Some of the blood drawn from you as part of this study may be used to screen for different types of viral liver infections, such as hepatitis. If the tests show evidence of hepatitis or other medical conditions, you will be informed of the results. If you do not have a regular physician, the study team will assist in referring you to an appropriate physician for evaluation.

GENETIC TESTING

Some of the blood drawn from you as part of this study will be used for genetic tests. Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Your blood sample used in these genetic tests will not have your name on it and the results will not be in your medical record. These tests are not used to check your health and we will not tell you the results.

<u>NIH Site only</u>: A special genetic test, called HLA typing, may be done by the NIH Clinical Center medical laboratory. These results will be in your medical record but they will not be used to check your health. Any genetic testing, including HLA typing, is for research purposes only. Any genetic information collected or learned about you will be kept confidential. Medical records, including HLA test results, are kept securely. We will not give any genetic information that is in your medical record to anyone without your permission.

If HLA typing is done in a research laboratory, the result will not be included in your medical record.

HIV TESTING

As part of this study, we will test you for infection with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. If you are infected with HIV you will still be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

STORED SAMPLES

To be eligible for the study, you must also be willing to allow some of your blood samples to be stored for future research on HIV disease, the immune system, or other medical conditions.

Generally, the results from the research done with your stored samples will not be given to your private doctor and will not be put in your medical record. This is because the test results, unlike routine medical testing, may be experimental or preliminary. The relevance of these tests to your care may be unknown. However, at your request, the results of any research tests will be discussed with you or your physician by one of the investigators.

Labeling of stored samples

Your stored samples will be labeled with a code (such as a number) that only the study team can link to you. Any identifying information about you will be kept confidential to the extent permitted by law.

Future studies

Your samples may be kept in storage for a long time and used in the future by medical researchers. When the study team shares your samples, they will share it with only a code on it. Some information about you, such as your gender, age, health history, or ethnicity may also be shared with other investigators.

Your stored materials will be used only for research and will not be sold or used for treating other people. The research done with your materials may be used to develop new products in the future, but you will not receive payment for such products.

RISKS

Blood drawing may cause pain, bruising, and, rarely, infection at the site where the blood is taken.

Collection of samples by swabs rubbing over the inside of the nose, inside the mouth vagina, penis or skin can cause temporary discomfort.

BENEFITS

There will be no direct benefit to you for participating in this protocol. The knowledge gained through this research may benefit others in the future.

UNKNOWN RISKS OR BENEFITS

Some routine medical tests may be performed during study participation. You may learn new information about your health. Receiving a new diagnosis may be stressful. You may feel that learning new information about your health is a benefit of study participation. Or you may feel this is a risk of study participation.

ALTERNATIVES

The study procedures are not being done to treat a medical condition. You may choose not to participate in any or all of the procedures discussed.

COMPENSATION

[Site specific information]

You will be compensated [insert amount] for blood samples collected by needle stick. Other payments for time and inconvenience of study visits may be offered in accordance with [insert institution] guidelines.

Compensation will be provided [add site-specific time for when compensation will be provided].

Total compensation is based on the number of study clinic visits and the type of sample collection performed. Your compensation may need to be reported to the Internal Revenue Service (IRS) as taxable income.

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study without your consent for the following reasons:

- The NIH doctor feels that staying in the study is harmful to you.
- The study is canceled or stopped.
- You don't keep appointments or follow study procedures.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for any of the costs that are directly related to this study. However, the costs of any other medical care you may need during this period will be your responsibility. You will not have to pay the cost of shipping the sample or completed forms.

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the [insert name of institution] will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the [insert name of institution] will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your [insert name of institution] medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **Policy Regarding Research-Related Injuries.** The [insert name of institution] will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, [insert name of institution], or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the [insert name of institution] policies. In general, patients are not paid for taking part in research studies at the [insert name of institution]. Reimbursement of travel and subsistence will be offered consistent with [insert name of institution] guidelines.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the principal investigator, [insert name] at [insert phone number], or Study Coordinator [insert name] at [insert phone number].
You may also call the Clinical Center Patient Representative at

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

Adult Patient's Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative ____ Date ____ Print Name ____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM [insert date] THROUGH [insert date].

Signature of Investigator ____ Date ____ Signature of Witness ____ Date ____

Print Name ____ Print Name ____

To: Baric, Ralph S[rbaric@email.unc.edu]
From: zlshi[zlshi@wh.iov.cn]
Sent: Thur 2/13/2020 3:26:25 AM (UTC-05:00)
Subject: virus name
A unique and unified name is needed for the novel coronavirus from Wuhan_SJ_clean.docx

Dear Ralph,

We heard that the 2019-nCoV was renamed as SARS-CoV-2. We had a fierce discussion among Chinese virologists. We have some comments on this name, I'm wondering if the CoV study group would consider a revision.

I attached the comments from me na dmy Chinese colleague.

Best regards,
Zhengli,

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430071 Wuhan, Hubei
China
Tel & Fax:
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Suggestion to the Coronavirus Study Group (CSG) of ICTV

A unique and unified name is needed for the novel coronavirus identified from Wuhan

An outbreak of unusual pneumonia of unknown cause in Wuhan, China was first reported in December, 2019. By 5 January, 2020, Chinese scientists had quickly identified the causative agent as a new type of coronavirus (CoV) belonging to the *Betacoronavirus* genus of the *Coronaviridae* family that also includes severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV (Zhu et al., 2020; Zhou et al., 2020; Wu et al., 2020; Chen et al., 2020). On 12 January 2020, the World Health Organization (WHO) temporarily named the virus as **2019 novel coronavirus (2019-nCoV)** (WHO webpage). On 30 January, WHO recommended naming the disease as "2019-nCoV acute respiratory disease" (WHO webpage). On 8 February 2020, the China National Health Commission (CNHC) announced naming the disease as **"Novel Coronavirus Pneumonia" (NCP)** (CNHC webpage). On 11 February 2020, WHO renamed the disease as "**coronavirus disease 2019" (COVID-19)** (WHO webpage). On 7 February 2020, the Coronavirus Study Group (CSG) of the International Committee on Virus Taxonomy (ICTV) posted a manuscript at bioRxiv and suggested designating the novel coronavirus as "**severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**" based on the phylogenetic analysis of related coronaviruses (Gorbalenya et al., 2020).

By 11 February 2020, the new coronavirus had caused more than 40,000 confirmed infections and more than 1000 deaths, mostly in mainland China, in spite of efforts by the Chinese government and its people to contain spread of the virus in past weeks. It goes without saying that the effects of the epidemic on all the aspects of Chinese life are devastating and, possibly, irreversible. Consequently, appropriately naming the virus and disease becomes a matter of importance to the Chinese people, in general, and virologists, in specific, and the issue has been fervently discussed and debated

among scientists with outcomes so far, as noted above. We fully agree that the new virus and SARS-CoV belong to the same virus species by classification. However, the consensus opinion of Chinese virologists is that none of the currently proposed names reflects the uniqueness and characteristics of the novel virus and that more consideration is needed for naming the virus. Based on the following reasons, we propose giving a unique and unified name to the new virus.

1. All proposed names are either too generic, or too similar, to previously well-known viruses, or contain an Arabic number. This makes it hard to remember or recognize, leading to a tendency among the general population and scientists alike to use a shorthand term such as “Wuhan coronavirus” or “Wuhan pneumonia”. This has, in fact, been the case since it was named as 2019-nCoV. This practice would, however, stigmatize and insult the people in Wuhan, who are still suffering from the outbreak.

2. The new virus has clinical, virological and epidemiological manifestations different from those of previously known coronaviruses, including SARS-CoV. Therefore, the name of the virus should be unique and characteristic to its identity. Phylogenetic analysis does show that the new virus and SARS-CoV, as well as many SARS-like-CoVs from bats and some intermediate hosts, belong to the same virus species (SARSr-CoV) (Guan et al., 2005; Ge et al., 2013; Zhou et al., 2020; Gorbalenya et al., 2020). Nonetheless, it is not appropriate to designate this new virus as SARS-CoV-2. First, if this new virus is named as SARS-CoV-2, then the previously known SARS-CoV should be renamed as SARS-CoV-1. This will lead bibliographic problems for the previous publications, and it is unnecessary. Second, the name SARS-CoV-2 does not reveal any apparent difference from SARS-CoV, thus misleading many into believing that it is just one type of SARS-CoV. This would, for example, lead many into thinking that the CFR of 2019-nCoV will increase to 10%, as it did for SARS, but this would cause worldwide panic and have a disastrous effect on the international economy. It might also be thought that a "SARS-CoV-2" epidemic will plateau by summer- time and be gone like the SARS virus. This may not be the case and may have adverse

effects on the implementation of the outbreak control activities.

3. The new virus is still evolving, and it is still too early to predict the outcome of the current outbreak. However, it is already clear that the infection of the new virus has diverse symptoms, from asymptomatic infection to severe pneumonia and even death. It has less case-fatality rate and higher transmissibility than SARS-CoV, indicating its clear difference from SARS-CoV. Again, therefore, it is not appropriate to designate the new virus as SARS-CoV-2 before we know more properties of the virus.

4. In consideration of the above reasoning and in view of the contagiousness and transmissibility of the new virus, we suggest proposing a unique and easy-to-use name for it, such as "**Transmissible acute respiratory coronavirus (TARS-CoV)**" (Jiang and Shi, 2020). Another choice is "**Human acute respiratory coronavirus (HARS-CoV)**. In this way, the new coronavirus and SARS-CoV, as well as related bat SARS-like coronaviruses, would, together, comprise the biological species of SARSr-CoV, which complies with the conventions of the classification and nomenclature of ICTV.

Proposers:

Zhengli Shi, Wuhan Institute of Virology, Chinese Academy of Sciences

Shibo Jiang, Fudan University School of Medicine

Wenjie Tan, China Center for Disease Control and Prevention

Yuelong Shu, Sun Yat-sen University, School of Public Health (Shenzhen)

Deyin Guo, Sun Yat-sen University School of Medicine

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Cc: shibojiang@fudan.edu.cn[shibojiang@fudan.edu.cn]; zlshi@wh.iov.cn[zlshi@wh.iov.cn]; Isabel Sola[isola@cnb.csic.es]; Leo Poon[llmpoon@hku.hk]; Baric, Ralph S[rbaric@email.unc.edu]; A.E.Gorbalenya@lumc.nl[A.E.Gorbalenya@lumc.nl]; b.haagmans@erasmusmc.nl[b.haagmans@erasmusmc.nl]; Sbaker1@luc.edu[Sbaker1@luc.edu]; bneuman@tamut.edu[bneuman@tamut.edu]; stanley-perlman@uiowa.edu[stanley-perlman@uiowa.edu]; R.J.deGroot@uu.nl[R.J.deGroot@uu.nl]; llmpoon@hkucc.hku.hk[llmpoon@hkucc.hku.hk]; christian.drosten@charite.de[christian.drosten@charite.de]
To: 郭德银[guodeyin@mail.sysu.edu.cn]
From: John Ziebuhr[john.ziebuhr@viro.med.uni-giessen.de]
Sent: Sat 2/15/2020 7:55:22 AM (UTC-05:00)
Subject: Re: virus name

Dear Dr. Deyin Guo, dear colleagues,
I am sorry to learn that I was not able to get my point across, which is that the name SARS-CoV-2 links this virus to other viruses (called SARS-CoVs or SARSr-CoVs) in this species including the prototype virus of the species rather than to the disease that once inspired the naming of this prototype virus nearly 20 years ago. The suffix -2 is used as a unique identifier and indicates that SARS-CoV-2 is yet ANOTHER (but closely related) virus in this species. I'd like to thank you for your comments because they indicate that we may need to explain our line of reasoning even more clearly when it comes to publishing a more advanced version of our manuscript.

As you again link virus classification and naming to specific diseases (as was unfortunately done quite frequently in the pre-genomic era) rather than to sequence relationships of the respective virus with previously identified viruses, I would like to ask you whether your reasoning implies that researchers describing all the other viruses in that species were wrong when they named the viruses they discovered? To my knowledge, the vast majority of these viruses has not been shown to cause a human disease called SARS and yet, they were called SARS coronaviruses or SARS-related coronaviruses in virtually all cases. I think it is accepted in the field that these viruses are genetically closely related but also differ in specific phenotypic aspects from one another, which is reflected (at the level of naming) by attaching pre- and suffixes to the (SARS-containing) virus name. When introducing the name SARS-CoV-2, the CSG followed the tradition established mainly by Chinese researchers to name viruses in this particular species.

With kind regards,

John Ziebuhr

—
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Schubertstr. 81, BFS
35392 Giessen, Germany
Phone:

Am 15.02.2020 um 07:32 schrieb 郭德银 <guodeyin@mail.sysu.edu.cn>:

Dear Dr. John and CSG members,

Thank you very much for your prompt reply and for your willingness to listen to us, the representatives of Chinese virologists in coronavirus studies.

After discussing with many members of the Chinese Society for Virology of Chinese Society for Microbiology, and the Sub-Society for Medical Virology of Chinese Medical Association, we still believe that SARS-CoV-2 is not the most appropriate name for 2019-nCoV.

You claimed that the CSG does not intend to make any reference to a specific disease (for example a severe respiratory disease in humans) when introducing yet another virus name derived from the term "SARS".

However, "SARS" is a disease name, and if the new virus is called SARS-CoV-2, it actually implies for SARS, especially for non-corona virologists and the public domain. In such sense, it is truly misleading. It is clear that there are significant differences in viral genome, transmissibility, and pathogenicity and pathogenesis of the diseases caused by 2019-nCoV and SARS-CoV. We are concerning about the name of a natural virus in one virus species, and we think that the natural virus should have its unique name to show some of its own properties. This is similar to the situation for Betacoronavirus 1, where the species includes several distinct natural viruses with their unique names, e.g. human OC43 and bovine coronavirus, and Alphacoronavirus, which includes distinct natural viruses like feline infectious peritonitis coronavirus, canine CoV and transmissible gastroenteritis coronavirus. It is not appropriate to use one disease-based virus' name (like SARS-CoV) to name all other natural viruses that belong to the same species but have very different properties.

To the best of our knowledge, none of the virologists from mainland of China attended the CSG's discussion on 2019-nCoV, and CSG had not consulted with virologists including the first discovers of the virus and first describers of the disease from mainland of China before making the decision. It is our wish that the CSG can take our opinion into the consideration.

It appears to us (as from the News reports of Science and Nature) that the CSG and WHO did not consult with each other in naming the virus and the disease. It will be very confusing to use totally different or unrelated names for the virus and its disease. We hope that the CSG of ICTV, the WHO and the Chinese side can have a trilateral negotiation on the naming issues.

Because of these reasons, we still hope CSG being able to reconsider naming 2019-nCoV. Our suggestion is to name it as TARS-CoV, but not SARS-CoV-2.

Thank you very much for your help!

Sincerely yours,

Deyin Guo, on behalf of the group:

Zhengli Shi, Wuhan Institute of Virology, Chinese Academy of Sciences
Shibo Jiang, Fudan University School of Medicine
Wenjie Tan, China Center for Disease Control and Prevention
Yuelong Shu, Sun Yat-sen University, School of Public Health (Shenzhen)
Deyin Guo, Sun Yat-sen University School of Medicine

-----Original Messages-----
From:"John Ziebuhr" <john.ziebuhr@viro.med.uni-giessen.de>
Sent Time:2020-02-14 22:26:34 (Friday)
To: guodeyin@mail.sysu.edu.cn, shibojiang@fudan.edu.cn, zlshi@wh.iov.cn
Cc: "Isabel Sola" <isola@cnb.csic.es>, "Leo Poon" <llmpoon@hku.hk>, "Baric, Ralph S" <rbaric@email.unc.edu>, "A.E.Gorbalenya@lumc.nl" <A.E.Gorbalenya@lumc.nl>, "b.haagmans@erasmusmc.nl" <b.haagmans@erasmusmc.nl>, "Sbaker1@luc.edu" <Sbaker1@luc.edu>, "bneuman@tamut.edu" <bneuman@tamut.edu>, "stanley-perlman@uiowa.edu" <stanley-perlman@uiowa.edu>, "R.J.deGroot@uu.nl" <R.J.deGroot@uu.nl>, "llmpoon@hkucc.hku.hk" <llmpoon@hkucc.hku.hk>, "christian.drosten@charite.de" <christian.drosten@charite.de>
Subject: virus name

Dear Deyin, dear Zhengli, dear Shibo, dear colleagues,

Thank you very much for sharing your thoughts with me and other members of the CSG. Obviously, I (personally) cannot speak for other CSG members but would like to tell you and your colleagues that I am very grateful for your very thoughtful and balanced statement.

I am pleased that you agree with the study group's decision to assign this newly discovered coronavirus to the species *Severe acute respiratory syndrome-related coronavirus*. The scientific basis for the assignment and naming has been laid out in the paper we recently published in a manuscript submitted to the bioRxiv preprint server and, at this stage, I cannot add much to this. There is one key point, however, that I would like to stress again: In their decision on the virus name, the CSG did not intend to make any reference to a specific disease (for example a severe respiratory disease in humans) when introducing yet another virus name derived from the term "SARS". The universal use of "SARS(r)" in names of viruses in this species just serves to underline the close genetic relatedness of these viruses. A large proportion of viruses in this virus species have been identified in bats and other animals in China and a few other countries, and virtually all these viruses were named SARS or SARS-related coronaviruses – most of them not because of their association with a disease (called SARS) in humans but because of their close genetic relatedness with a previously described VIRUS (called SARS-CoV) and clearly NOT the DISEASE that this particular virus caused. This (and nothing else) was the reasoning behind the study group's decision to continue the naming tradition established by researchers studying animal and human viruses of this virus species.

In a slightly different context, I would like to point out that it is not within the remit of the CSG to decide on names for clinical manifestations, progression, transmissibility etc. of coronavirus-associated diseases. This lies within the responsibility of WHO. Obviously, Chinese clinicians involved in the clinical management of patients infected with SARS-CoV-2 would be in the best position to provide advise to WHO officials on that matter. On a more personal note (and outside my role as member of the ICTV and chair of the CSG), I feel that your suggestion to name the disease "Transmissible acute respiratory syndrome (TARS)" could be a very good starting point for discussions with WHO. In my opinion, the recently introduced disease name COVID-19 could be improved and I would encourage you to enter or renew discussions with WHO on this matter.

I very much hope that I was able to convince you that the CSG's decision on this particular virus name was made with the very best intentions and based purely on SCIENTIFIC judgement. Personally, I feel reassured by the positive response I have been receiving over the past few days from other colleagues, ICTV, NCBI and other players and believe that the CSG has made a decision that will facilitate future communication among virologists studying these viruses. As part of these efforts, the CSG also suggested a naming convention to be used for specific SARS-CoV-2 isolates (and other coronavirus isolates).

With many thanks and kind regards,

John Ziebuhr

—
Prof. Dr. John Ziebuhr
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Germany
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To: Walters, William[WaltersWA2@state.gov]; Baric, Ralph S[rbaric@email.unc.edu]; Richard Hatchett[richard.hatchett@cepi.net]; Carter Mecher |; Lawler, James V[james.lawler@unmc.edu]; Callahan, Michael V.,M.D.[MVCALLAHAN@mgh.harvard.edu]; Lisa Koonin ; Hepburn, Matthew J CIV USARMY (USA)[matthew.j.hepburn.civ@mail.mil]; David Marcozzi[DMarcozzi@som.umaryland.edu]; 'Martin, Gregory J (MartinGJ@state.gov)'[MartinGJ@state.gov]; Kadlec, Robert (OS/ASPR/IO)[Robert.Kadlec@hhs.gov]; jwleduc@UTMB.EDU[jwleduc@UTMB.EDU]; Eastman, Alexander[alexander.eastman@hq.dhs.gov]; HARVEY, MELISSA[melissa.harvey@hq.dhs.gov]; Anthony Fauci (afauci@niaid.nih.gov)[afauci@niaid.nih.gov]
From: Caneva, Duane[duane.caneva@hq.dhs.gov]
Sent: Sat 2/15/2020 6:15:51 PM (UTC-05:00)
Subject: RE: Flash!! Red Dawn Call Re: Air Evacuation Risk Mitigation Measures
Solitude Brief Updated.pptx
FINAL 2018 Tranquil Terminus FSE AAR_20July2018.pdf

Some background on air evac.

-----Original Appointment-----
From: Caneva, Duane
Sent: Saturday, February 15, 2020 1:04 PM
To: Caneva, Duane; Walters, William; Baric, Ralph S; Richard Hatchett; Carter Mecher; Lawler, James V; Callahan, Michael V.,M.D.; Lisa Koonin; Hepburn, Matthew J CIV USARMY (USA); David Marcozzi; 'Martin, Gregory J (MartinGJ@state.gov)'; Kadlec, Robert (OS/ASPR/IO); jwleduc@UTMB.EDU; Alexander Eastman (Alexander.Eastman@hq.dhs.gov); MELISSA HARVEY (melissa.harvey@hq.dhs.gov)
Subject: Flash!! Red Dawn Call Re: Air Evacuation Risk Mitigation Measures
When: Saturday, February 15, 2020 6:00 PM-7:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where

Purpose: Discuss risk mitigation measures for COVID-19 transmission during flight operations.
Please extend to appropriate experts with discretion.

PROJECT SOLITUDE

Biocontainment MEDEVAC in a New Era…

Directorate of Operational Medicine
U.S. Department of State

PROJECT OBJECTIVES

Provide an on-call aircraft service for use by the Department to perform emergency movement of personnel and retrieve critically ill or injured personnel, including personnel infected with unique and highly communicable pathogens.

LESSONS LEARNED

- Immediate goal was to transport Ebola-stricken patients across international borders without worsening their condition or exposing others to infection.

- To do so, the Department of State contracted a specialized plane through Phoenix Air Group. The Department of State team--in partnership with HHS and the U.S. Centers for Disease Control and Prevention (CDC)--coordinated the evacuation of personnel from multiple countries infected with or exposed to the Ebola virus.

PROJECT IDENTIFICATION AND PURPOSE

- The purpose of Project Solitude is to provide the U.S. Department of State with the capability of transporting response personnel and retrieving critically ill personnel safely, swiftly, and securely to and from locations anywhere in the world, in the most expeditious manner.

PROJECT IDENTIFICATION AND PURPOSE

- The aircraft is configured to rapidly deploy an Intensive Care air ambulance capability on short notice, while isolating a highly contagious pathogen. This program addresses what had been a critical capability gap across the inter-agency community that left USG and partnered personnel vulnerable to naturally occurring and man-made pathogen outbreaks.

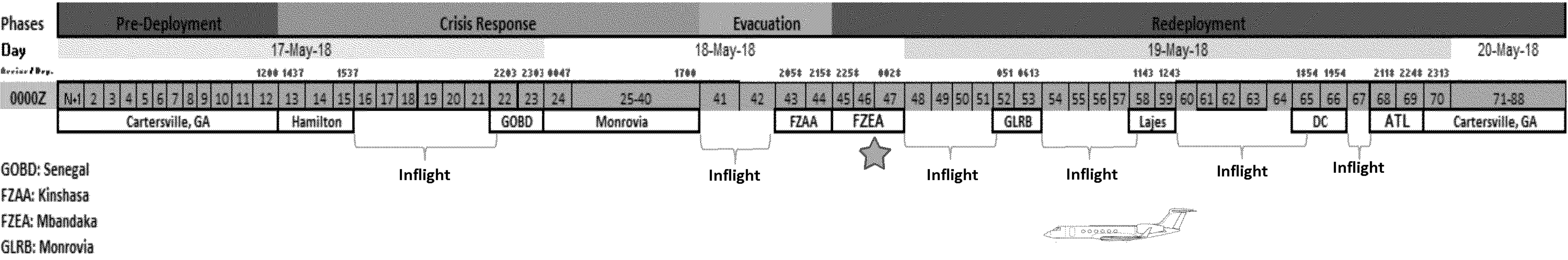
DEDICATED ON CALL AIRCRAFT

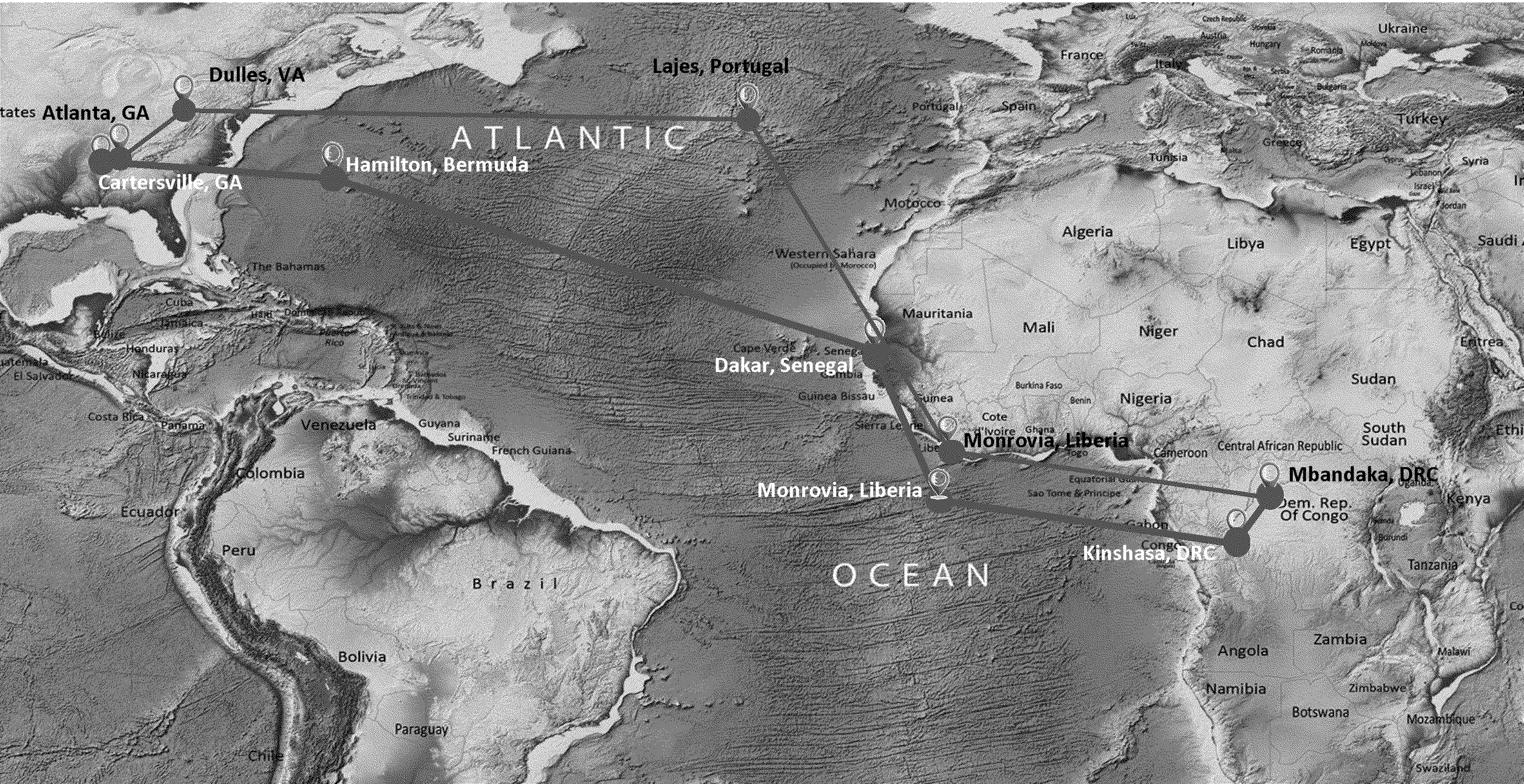
- Each charter flight performed for the Department is ordered on an individual "Service Call" against a fully funded contract.

- A fixed price, based on flight particulars is estimated at the outset of the mission.

- At the completion of the mission, an invoice is prepared for the flight costs, based on negotiated fixed rates for each portion of a flight hour.

Mission (Ebola Response Plan): Mbandaka, DRC May 2018





HOW TO REQUEST

If highly communicable pathogen, mass casualty or need for rapid movement for a critical care patient…

Contact Operational Medicine (+1-202-644-8142): Prioritization of cases critical through MED/DMD/OM because this capability is the sole resource for highly contagious pathogens. Management and control of the deployment of the resource is through our office.

Dr. Walters is Contracting Officer's Representative for the contract. Mr. Patrick Corcoran is the Assistant Contracting Officer's Representative. Either can authorize and control the mission.

WHAT WE NEED FROM YOU

- Point of contact with phone number at the referring post
- Mission origin
- Patient report
- Patient passport
- Mission destination
- Originating post provides logistics and patient transport to airport.
- Accepting post provides logistics and patient transport to the hospital.

WHAT WE OWE YOU

- OM will look at current deployments and provide authorization for your mission through the COR if no other mission conflicts.
- OM will contact PAG for a quote and itinerary and will forward this to the requesting RMO or MP at the originating post and the POC at the accepting medevac center.
- OM will provide updates on any changes in launch time or delay in flight time itinerary to the POC at originating post and accepting medevac center.
- If questions arise during the medevac, contact Dr. Walters, or the designated OM POC. Do not contact Phoenix.

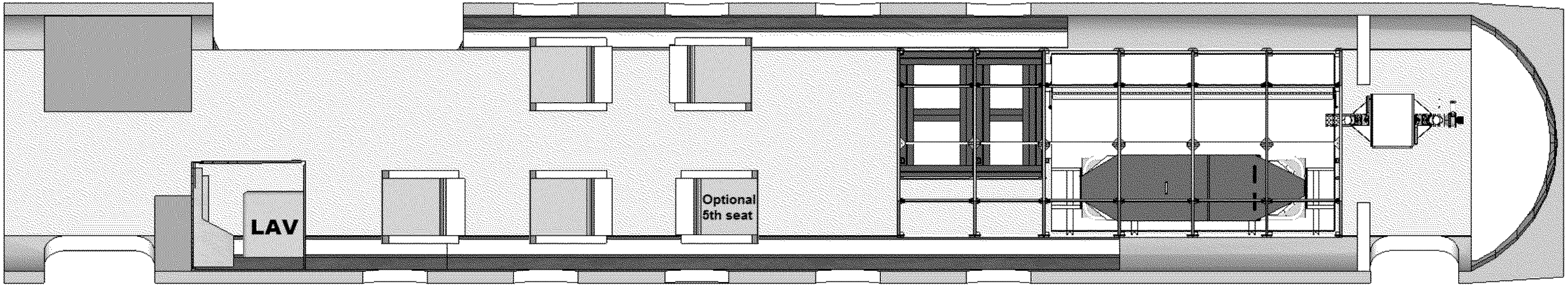
CONTAINERIZED BIO-CONTAINMENT SYSTEM (CBCS)

TFT color monitor
V1/V2
MENU
-
+

AIRBORNE BIO-CONTAINMENT SYSTEM (ABCS)

Department of State - N163PA

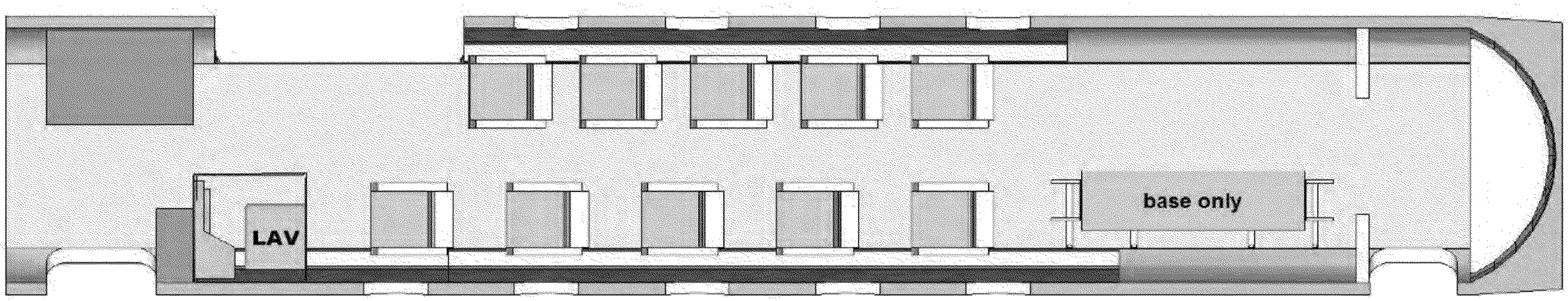
ABCS
4 passengers
5 passengers optional



Two seats must face ABCS

Department of State - N163PA

10 passengers



TRANQUIL TERMINUS

- The 2018 Tranquil Terminus Full-Scale Exercise (FSE) was a four-day, multi-state exercise co-sponsored by HHS/ASPR, DOS to test the nation's ability to domestically move HID patients safely and securely from various healthcare facilities to Regional Ebola Treatment Centers (RETCs).
- The Tranquil Terminus FSE brought together over 50 local, state, regional, federal, private sector, and nongovernmental organizations and focused on the notification processes, coordination decisions, and resources needed to move HID patients utilizing both air and ground transportation resources.

TRANQUIL TERMINUS

- Over the course of the exercise, seven patients—including one pediatric patient—presented to healthcare facilities with Ebola-like symptoms.
- Each patient received a positive laboratory diagnosis for Ebola Virus Disease (EVD), which triggered a series of notification and coordination processes among local, state, federal, private sector, and nongovernmental partners to facilitate the movement of these patients to RETCs.

TRANQUIL TERMINUS

- Transportation was provided by various ground ambulance agencies along with air assets provided by DOS vendors. Six of the seven patients were moved across state boundaries—two of the six were moved across regional boundaries—providing HHS an opportunity to examine and synchronize inter- and intra-regional HID patient movement plans and capabilities.

Tranquil Surge logistics

- During the exercise, the CBCS was loaded onto a chartered 747 aircraft. The aircraft picked up willing participants role-playing as infected Ebola patients in Monrovia, Liberia and brought them to the University of Nebraska Medical Center.
- As part of the drill, participants from multiple countries, agencies, and local governments tested their procedures--everything from the mechanics of the actual container to the process for communicating across agencies and receiving clearances to bring the ill individuals across jurisdictions.
- Exercises like this one ensure we are prepared to respond immediately to an emerging infectious disease threat anywhere in the world.

Questions?

Questions?

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

2018 TRANQUIL TERMINUS FULL-SCALE EXERCISE AFTER-ACTION REPORT

JUNE 2018

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

FOR OFFICIAL USE ONLY

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HANDLING INSTRUCTIONS

1. The title of this document is the *2018 Tranquil Terminus Full-Scale Exercise After-Action Report*.
2. Information gathered in this After-Action Report is designated as For Official Use Only (FOUO) and should be handled as sensitive information that is not to be disclosed. This document should be safeguarded, handled, transmitted, and stored in accordance with appropriate security directives. Reproduction of this document, in whole or in part, without prior approval from the U.S. Department of Health and Human Services (HHS) is prohibited.
3. At a minimum, the attached materials will be disseminated strictly on a need-to-know basis and, when unattended, will be stored in a locked container or area that offers sufficient protection against theft, compromise, inadvertent access, and unauthorized disclosure.
4. For more information about the exercise, please consult the following points of contact:

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EXECUTIVE SUMMARY

During the 2016 Ebola response efforts, the capability to safely and securely transport infectious patients was identified as an area for improvement. Since the conclusion of these response efforts, the nation has worked diligently to increase its capability and capacity to move infectious patients—necessitating conduct of a series of infectious disease patient movement exercises to validate current processes. Building upon the U.S. Department of State's (DOS) Tranquil Shift Exercises that tested advances in biocontainment transport equipment and coordination efforts to move highly infectious disease (HID) patients from overseas to treatment centers within the U.S., the U.S. Department of Health and Human Services (HHS) / Office of the Assistant Secretary for Preparedness and Response (ASPR) developed the Tranquil Terminus Exercise Series as a platform to engage states, HHS regions, federal Emergency Support Function (ESF) #8 patient movement partners, the private-sector, and non-governmental organizations (NGOs) to examine HID patient movement operations within the U.S.

The 2018 Tranquil Terminus Full-Scale Exercise (FSE) was a four-day, multi-state exercise co-sponsored by HHS/ASPR, DOS as well as Georgia, South Carolina, Oklahoma, Texas, California, Idaho, and Washington State to test the nation's ability to domestically move HID patients safely and securely from various healthcare facilities to Regional Ebola Treatment Centers (RETCs). The Tranquil Terminus FSE brought together over 50 local, state, regional, federal, private sector, and nongovernmental organizations and focused on the notification processes, coordination decisions, and resources needed to move HID patients utilizing both air and ground transportation resources. The exercise began on April 9, 2018 and concluded on April 12, 2018.

Over the course of the exercise, seven patients—including one pediatric patient—presented to healthcare facilities with Ebola-like symptoms. Each patient received a positive laboratory diagnosis for Ebola Virus Disease (EVD), which triggered a series of notification and coordination processes among local, state, federal, private sector, and nongovernmental partners to facilitate the movement of these patients to RETCs. Transportation was provided by various ground ambulance agencies along with air assets provided by DOS vendors. Six of the seven patients were moved across state boundaries—two of the six were moved across regional boundaries—providing HHS an opportunity to examine and synchronize inter- and intra-regional HID patient movement plans and capabilities.

Approximately 100 controllers and evaluators from participating organizations deployed to key sites across the nation—including hospitals, airfields, state and local emergency operations centers, and the HHS Secretary's Operations Center (SOC)—to control and

observe exercise play as well as to record observations related to exercise discussions, activities, and decisions. In addition, HHS assigned an evaluator to accompany each patient throughout the exercise to observe activities from the originating facility to the accepting RETC. Following the exercise, evaluators participated in hotwashes at their respective venues, and HHS facilitated a virtual hotwash with all partners to gather high-level observations on the following topic areas: communication and coordination processes; patient transport; and patient care. HHS also gathered player feedback using the HHS/ASPR/Office of Emergency Management/Training, Exercises, and Lessons Learned Branch Corrective Action Program Electronic Feedback Form.

The Evaluation Team compiled all exercise data to produce an objective, time-based account of what happened during the exercise, comparing decisions and actions against applicable plans, policies, and procedures to identify gaps and issues. The purpose of this report is to provide an overview of the exercise, identify strengths and areas for improvement, and provide actionable recommendations to improve the nation's ability to safely and securely move HID patients domestically.

Major Strengths

The Tranquil Terminus FSE provided partners an opportunity to test lessons learned from the 2014 Ebola crisis and identify strengths to be maintained and built upon. The major strengths from the exercise are listed below.

- Facility plans include protocols to successfully minimize the risk of disease spreading to facility staff and others.
- The FAA provided the HHS SOC with timely flight status updates, allowing ground transport crews to ensure that their equipment and personnel were staged and prepared for patient handoff.
- Patient movement partners successfully implemented a variety of technologies—including livestreaming, videoconferencing, and GPS tracking—to prepare providers to receive the patient(s) and enhance situational awareness during patient transport.
- "High risk" ambulances enhanced the safety and efficiency of HID patient transport.
- Hospitals and EMS providers were well-supplied with PPE for their personnel and patients.
- Patient care teams quickly implemented procedures to monitor personnel who had direct contact with HID patients.
- Hospitals successfully and safely collected, packaged, and simulated shipment of patient specimens to state public health laboratories for testing.

Primary Areas for Improvement

The Tranquil Terminus FSE also revealed several areas for improvement related to HID patient movement plans, processes, and procedures. Primary areas for improvement are listed below.

- Overall, HID patient movement plans are not synchronized between or among, local, state, regional, and federal stakeholders.
- The lack of clear, coordinated multi-regional patient movement protocols hampered the ability of partners to coordinate effectively.
- Federal and regional HID patient movement plans do not include the timeline for notification, activation, and employment of DOS vendor aircraft(s) in support of domestic HID patient movement.
- Coordination calls do not align and confusion regarding their purpose, logistics, and timing hampered the ability of providers to focus on patient care.
- There was confusion among patient movement partners about when it is appropriate to discuss PII on coordination calls.
- Local, state, and federal patient movement partners were not fully knowledgeable on initial notification processes upon receipt of a person under investigation (PUI(s)).
- Patient care providers were uncertain of how and when to initiate direct provider-to-provider communication during the patient transfer coordination process.
- Existing protocols for communication between DOS vendor medical staff and medical staff at sending and receiving hospitals before and during patient transport were insufficient for maintaining situational awareness of the patient during aerial movement.
- Hospitals and EMS providers were unfamiliar with DOS vendor patient transfer protocols, which hampered their ability to plan for and seamlessly execute patient handoff.
- Improper ambulance preparation compromised patient health and safety.
- Some facilities do not routinely inspect equipment required to care for and transport HID patients.
- Mock ZMapp™ vials were successfully deployed to RETCs but experienced minor travel delays, shipment errors, and dosage miscalculations.
- The lack of standardized PPE requirements across the country resulted in various, inconsistent techniques being utilized posing challenges throughout patient movement operations.
- Inclement weather affected the ability of EMS personnel to don and doff PPE at airfields and increased the risk of contamination during patient handoff between EMS providers and DOS vendor medical crews.

- Exercise participants identified the need for defined protocols to assist in determining whether a security escort should be used for HID patient transport.

EXERCISE OVERVIEW

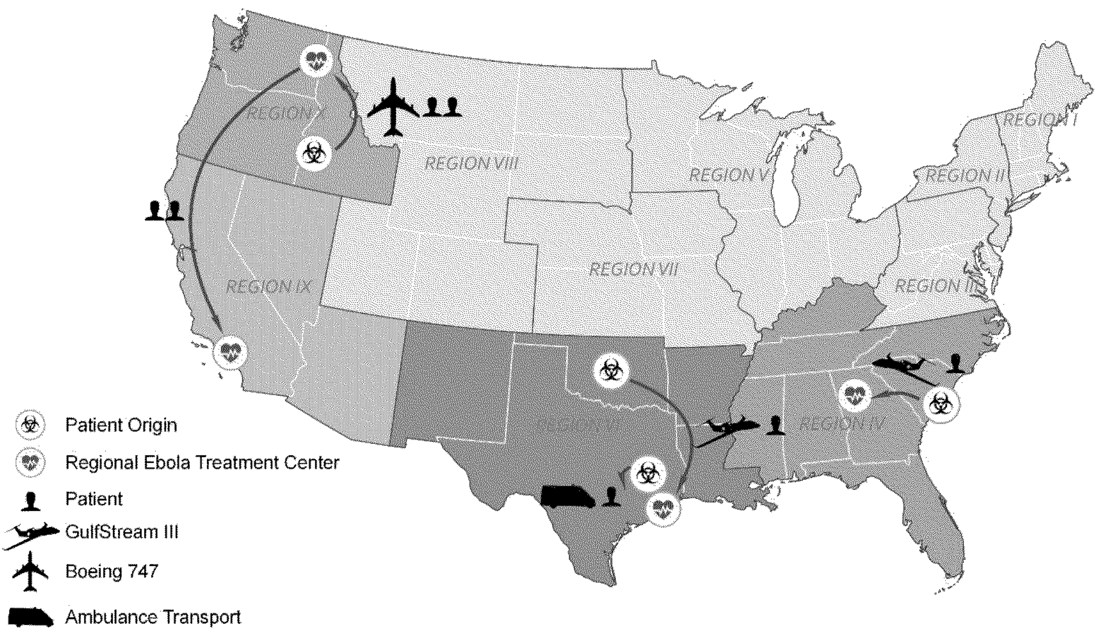
Exercise Name	2018 Tranquil Terminus FSE
Exercise Dates	April 9 – 12, 2018
Scope	The exercise included limited field play over a four day period at multiple venues in seven states. For a full list of field locations, see **Appendix B**.
Mission Area(s)	Response
Core Capabilities	• Planning • Operational Coordination • Critical Transportation • Logistics and Supply Chain Management • Public Health, Healthcare, and Emergency Medical Services
Hospital Preparedness Program Capabilities	• Foundation for Health Care and Medical Readiness • Health Care and Medical Response Coordination • Continuity of Health Care Service Delivery • Medical Surge
Overarching Exercise Objectives	• Engage local, state, regional, and federal interagency partners in the movement of HID patients. • Conduct interagency and intergovernmental coordination in the movement of HID patients. • Synchronize and validate current local, state, regional, and federal, and private sector standard operating procedures (SOPs) and plans associated with the domestic movement of HID patients. • Refine air and ground transportation protocols in the movement of HID patients.
Overarching Exercise Outcomes	• Test, validate, and update protocols for notification of movement of HID patients. • Further define and capture protocols for coordinating movement of HID patients. • Compare response actions and decisions during the exercise to validate applicable local, state, regional, and federal HID patient movement plans.
Threat or Hazard	Highly Infectious Disease

Scenario	Several individuals from a national, faith-based organization were working in remote communities in Liberia as part of a missionary trip and have since returned to their respective residences in Idaho, Oklahoma, Texas, and South Carolina. Two weeks following their return home, seven individuals were admitted to their local hospitals and diagnosed, through laboratory confirmation, with Ebola. On April 9, 2018, four patients were laboratory-confirmed with Ebola in Boise, Idaho. This began a series of notification and coordination processes among local, state, federal, nongovernmental, and private sector partners to facilitate the movement of these patients to RETCs. On April 11, 2018, an additional three patients—one pediatric and two adults—were laboratory-confirmed with Ebola. The pediatric patient was located in The Woodlands, Texas. The adult patients were located in Charleston, South Carolina and Norman, Oklahoma. Immediately following the laboratory confirmations, partners began a series of notification and coordination processes to move these patients from their respective originating facilities to RETCs.
Participants	For a full list of participating organizations, see **Appendix E**.

SUMMARY OF KEY EXERCISE EVENTS

The Tranquil Terminus FSE was conducted on April 9 – 12, 2018 and included full-scale field operations in Regions IV, VI, IX, and X. Figure 1 depicts the movement of each exercise patient. This section details a summary of key exercise events that occurred within each region. It is important to note that the exercise was designed with time compressions to allow participating organizations to meet their desired objectives within the time frame allotted for the exercise. Consequently, the time elapsed between events during the exercise may differ, in some cases significantly, from what would occur in a real-world response to moving patients with Ebola.

Figure 1. Tranquil Terminus FSE HID patient movement schema



Regions IX and X

On Monday, April 9, two adult patients presented to St. Luke's Eagle Urgent Care in Boise, Idaho with Ebola-like symptoms.[1] The patients were transported to St. Luke's Regional Medical Center (hereafter referred to as "St. Luke's") and placed in isolation. Concurrently, two additional adult patients presented to the Emergency Department (ED) at Saint Alphonsus Regional Medical Center with symptoms of Ebola and were

[1] For exercise purposes, one patient presented at St. Luke's and the additional patient was simulated on Monday. Both patients were present and packaged for transport on Wednesday morning.

placed in isolation at Saint Alphonsus. On the evening of April 9, all four patients were laboratory confirmed with Ebola.

Throughout the day on Tuesday, April 10, communication and coordination took place among local, state, federal, private sector, and NGO partners to arrange the movement of the Idaho patient cluster to RETCs. Two of the patients—a married couple—were accepted to Providence Sacred Heart Medical Center (PSHMC) in Spokane, Washington, and the remaining two patients were accepted to Cedars-Sinai Medical Center (CSMC) in Los Angeles, California.

Figure 2. Mock patients board Boeing 747 at Boise Airport

On the morning of Wednesday, April 11, the four patients were transported by ground ambulance from their originating facilities to Boise Airport, where they were loaded onto a Boeing 747 aircraft. The aircraft, carrying all four patients, first stopped at Spokane International Airport to offload the two patients bound for PSHMC. The aircraft then continued to Los Angeles International Airport to offload the two patients bound for CSMC. At each airport, DOS vendor clinicians handed the patients off to EMS personnel for transport to their respective RETCS. Hospital staff received the patients upon their arrival at their respective RETCs, and exercise conduct in Regions IX and X concluded on the evening of April 11.

Region IV

Figure 3. Mock patient boards DOS vendor's Gulfstream III at Charleston Airport

On Tuesday, April 10, an adult patient presented to an outpatient clinic at the Medical University of South Carolina (MUSC) in Charleston, South Carolina with symptoms of Ebola. The patient was placed in isolation at MUSC and was laboratory-confirmed with Ebola that evening. On Wednesday, April 11, communication and coordination took place among local, state, federal, private sector, and NGO partners to determine whether the patient should be transported to an RETC. The National Weather Service issued a Hurricane Watch for southeast South Carolina, prompting the decision to transport the patient from MUSC to Emory University Hospital (EUH) in Atlanta, Georgia.

On the morning of Thursday, April 12, the patient was transported by ground ambulance to Charleston Airport, where she was loaded onto a DOS vendor Gulfstream III aircraft for transport to Dekalb-Peachtree Airport just northeast of Atlanta, Georgia. At Dekalb-Peachtree Airport, DOS vendor clinicians handed the patient off to EMS personnel for transport to EUH. EUH clinicians received the patient, and exercise conduct in Region IV concluded on the afternoon of April 12.

Region VI

On the morning of April 11, a pediatric patient, accompanied by his father, presented to CHI St. Luke's Health–The Woodlands Hospital with symptoms of Ebola. The patient was placed in isolation at the hospital. Following laboratory confirmation of Ebola, local, state, and regional partners coordinated to arrange the movement of the patient to Texas Children's Hospital (TCH) West Campus in Houston, Texas.

On Wednesday afternoon, an adult patient presented to the ED at Norman Regional Hospital in Norman, Oklahoma. The patient was placed in isolation at Norman Regional Hospital. Following laboratory confirmation of Ebola local, state, federal, private sector, and NGO partners coordinated to arrange the movement of the patient to the University of Texas Medical Branch (UTMB) in Galveston, Texas.

Figure 4. Ambulance prepares for departure from Ellington Airport to UTMB

On the morning of April 12, the pediatric patient and his father were transported by ground ambulance to TCH, where the patient was received by TCH clinicians. Concurrently, the adult patient was transported by ground ambulance to Will Rogers World Airport, where she was loaded onto a DOS vendor Gulfstream III aircraft for transport to Ellington Airport. At Ellington Airport, DOS vendor clinicians handed the patient off to EMS personnel for transport to UTMB. UTMB clinicians received the patient, and exercise conduct in Region VI concluded on the afternoon of April 12.

KEY FINDINGS

This report identifies strengths and areas for improvement related to the ability to safely and securely move domestic HID patients by ground and air. The findings are organized by the following core capabilities: Planning; Operational Coordination; Critical Transportation; Logistics and Supply Chain Management; and Public Health and Medical Services. Recommendations are derived from feedback provided by exercise evaluators, players and subject matter expert observers.

1. Planning

Conduct a systematic process engaging the whole community as appropriate in the development of executable strategic, operational, and/or tactical-level approaches to meet defined objectives.

Aligned HPP Capabilities: Foundation for Health Care and Medical Readiness; Health Care and Medical Response Coordination

Observation 1.1: Overall, HID patient movement plans are not synchronized between or among, local, state, regional, and federal stakeholders.

Throughout the exercise planning process, HID patient movement partners detailed the process flow for each patient movement operation using current local, state, regional, federal and private-sector plans. In doing so, the planning process exposed several gaps in and discrepancies among all levels of HID patient movement partners as each agency/organization has their own plan. During the exercise, these gaps directly impacted the ability of partners to efficiently and effectively move HID patients. The following section details this information.

- **Plans are created in silos and not widely socialized among HID patient movement stakeholders.** The exercise planning process as well as exercise conduct illustrated that HID patient movement partners are not well versed with other partners' patient movement plans. For example, partners at all levels were unfamiliar with HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018). Similarly, some regional plans were undergoing revisions to their current HID patient movement planning processes and procedures which were not widely socialized prior to the exercise.
- **Plans for moving an HID patient do not include the process(es) to request federal patient movement assets.** While the HHS SOC received emails from HHS regional emergency coordinators (RECs) with initial notification of PUIs and

situational awareness updates, the emails did not include an explicit request from the state for federal aeromedical patient movement assistance. Although this may be an exercise artificiality—as participants knew prior to the exercise that HHS would provide assistance and DOS would provide aircrafts through vendor contracts—emails to the HHS emergency management group (EMG) Task Force Lead were often ambiguous or did not explicitly indicate that the state was requesting federal assistance. As a direct result, the HHS EMG Task Force Lead had to reach back out to HHS RECs for clarification on the state's capabilities and their expectations for support. Similarly, patient movement partners were unclear as to the roles and responsibilities of the HHS RECs versus the HHS Field Project Officers (FPOs). HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018) does not delineate between the roles and responsibilities of RECs and FPOs rather, they are described as one position instead of two separate positions with distinct roles and responsibilities.

- **Plans lack information on the notification and communication processes with state governors and key federal partners.** Although not directly examined during the exercise, patient movement partners highlighted the importance of including state governors in the notification of PUIs, as well as the movement of an HID patient(s) into or out of their respective states. An examination into federal and regional plans revealed a lack of information and guidance on this process. Furthermore, the HHS SOC's communication with other key federal partners, including initial notification of PUIs and subsequent coordination of federal assistance, was based solely on personal relationships. For example, during the exercise, the HHS EMG Manager communicated with DOS and NETEC partners based on previously established relationships. Although these relationships allowed for smooth communication and coordination, these processes should not be driven by individual relationships. Establish processes to communicate by position vice personal relationships.

Recommendation(s):

- Overall, HHS/ASPR as well as all HID patient movement partners should share their agency/organization-specific plans, policies, procedures with all partners to ensure socialization.
- To further enhance the usefulness and effectiveness of HHS's *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018), HHS/ASPR should consider implementing the following changes:
  - Move Step 19—when the DOS vendor aircraft departs to pick-up a patient—later in the process, as the Large Call occurs prior to the aircraft's departure;

  - Include any newly amended agendas for the Small Call and the Large Call within the body of the *SOP*;
  - Amend the language in Step 8 by specifying that consultation with NETEC is only necessary for inter-regional patient movement;
  - Move the Clinical Call (Step 15) earlier in the process and consider adding another one immediately prior to the patient(s) boarding the DOS vendor aircraft;
  - Update the agenda of the clinical call to ensure that participants discuss how the patient(s) will be packaged for transport;
  - Amend the purpose of the Logistical Coordination Call (Step 13), as this should occur for both inter-regional and intra-regional patient movement;
  - Eliminate Step 21 or combine it with Step 23, as the flight itineraries are provided during the Large Call; and,
- HHS/ASPR should update SOPs and/or job assistance guides to ensure there is uniformity in the way tasks are implemented and a clear process for communicating with other federal partners when coordinating the movement of HID patient(s).

- HHS/ASPR should include the process(es) to communicate with and seek a state governor's approval to move a HID patient into or out of his/her state into HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018).

- HHS RECs should collaborate with states to develop the exact processes and mechanisms to request federal aeromedical patient movement assistance and document these processes in their respective HID patient movement plans. HHS/ASPR should also consider including this information in HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018) to ensure that there is a universal understanding of HHS's expectations in making a request for federal assistance.

- HHS/ASPR should collaborate with RECs and FPOs to clarify and define their respective roles and responsibilities in HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018).During the exercise, it was suggested that the FPOs' intimate knowledge of their local hospitals' capabilities would be beneficial in facilitating the process of moving HID patients.

- HHS/ASPR should collaborate with HHS RECs to develop an overview of region-specific roles and responsibilities. These overview documents should be approved by the grant awardee, as well as by all of the states within each region. Once complete, they should be included as annexes in HHS's draft *Coordination*

Flow of Patients Infected with Highly Contagious Pathogens SOP (February 2018).

Observation 1.2: The lack of clear, coordinated multi-regional patient movement protocols hampered the ability of partners to coordinate effectively.

During the exercise, patient movement partners encountered challenges with multi-regional coordination due to gaps and unsynchronized processes in regional and federal plans. On the first day of the exercise, four PUIs in Boise, Idaho were diagnosed with EVD, which triggered a series of notification, coordination, and decision processes to move the patients to multiple RETCs. The Region X RETC—PSHMC—accepted two of the four patients, requiring Idaho partners to: (1) request federal assistance in identifying another RETC for the remaining two patients; and (2) request federal assistance in moving the patients by air. Regional and federal partners took the following steps to assist in coordinating the movement of the remaining two patients:

1. The Region X Regional Emergency Coordinator (REC) contacted the HHS SOC to request assistance in identifying a receiving RETC for the additional two patients;
2. The HHS SOC contacted NETEC for guidance on where to send the two patients—which RETCs are ready and capable to receive patients; and,
3. NETEC recommended sending the two patients to the Denver Health Medical Center in Denver, Colorado, due to its geographic proximity to the originating facility. For the purpose of the exercise, the HHS White Cell injected that The Denver Health Medical Center was unavailable and the decision was made to send the two patients to CSMC.

In order to move all four patients to their respective RETCs, federal and Region IX and X partners were required to simultaneously coordinate intra- and inter-regional patient movement. This proved challenging for the reasons detailed below.

- **No specific guidance exists for coordinating the movement of a cluster of HID patients.** HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018) provides a list of 36 coordination activities required to move a single patient from an originating facility to an RETC, focusing specifically on the responsibilities of HHS and other federal partners. The plan does not address how coordination activities will differ when federal partners are asked to move a cluster of patients to multiple RETCs. Although HHS/ASPR has a *Draft ASPR Highly Infectious Disease Cluster Plan* (December 2015), the document was not utilized or referred to during the exercise indicating that it is not socialized and that responders are not trained on its use as a reference.. Additionally, it was initially unclear to partners whether some of the federally-led coordination calls listed in the plan, such as the Large

Call, would be held separately for the PSHMC-bound and CSMC-bound patients or combined. The HHS SOC ultimately held a combined Large Call with all Region IX and X partners, but identified the need to update the plan to specifically address multi-regional coordination.

- **Partners were unclear which agency/organization was responsible for coordinating multi-regional HID patient movement.** Throughout the exercise planning process as well as the exercise, patient movement partners were unclear on the authorities of local, state, regional, and federal partners. Region IV and X plans specify that responsibility for coordinating inter-regional patient movement lies with the sending state's authorized coordinating agency, the receiving state's authorized coordinating agency, and partner federal agencies; however, neither plan describes the processes by which this coordination should occur. The Region VI and IX plans do not specify which entities will be responsible for coordinating inter-regional patient movement, nor do they describe inter-regional coordination processes. To address this gap, partners identified the need to engage all regions in developing a standardized framework for inter-regional coordination that can be incorporated into regional plans. Participants also emphasized the importance of clearly defining the role of the federal government in managing inter-regional coordination.
- **Plans do not clearly define the process for identifying a receiving RETC for each patient within the cluster.** According to the Region IV, VI, IX, and X HID patient movement plans, if the region's designated RETC cannot accept or is not willing to accept a patient, the HHS REC will notify the HHS SOC to assist the sending jurisdiction in identifying an alternate receiving RETC. During the exercise, the Region X REC followed this protocol in helping to identify CSMC as a potential destination for the two additional Idaho patients. While an additional RETC was identified for the remaining patients, patient movement partners were still unclear as to the decision process for determining which patients would be sent to each of the facilities and what agency/organization has the authority to make that determination. HHS/ASPR consulted with NETEC during the exercise to determine an additional RETC capable of accepting and treating two patients. While HHS/ASPR contacted NETEC during the exercise, the HHS SOC did not have the NETEC 24/7 access number—contact with NETEC was initiated through personal relationships.[2] Partners discussed numerous factors during the exercise that determine receiving RETCs such as: patient acuity, geographic proximity, patient preference, and patient relationship (if the two patients are

[2] The HHS SOC noted this as an after-action and NETEC shared the access number following the exercise.

related, the decision was unanimous to transport them together). While these topics were discussed at length during the exercise, no finite decision was made on what RETC would receive each set of two patients. As such, the HHS White Cell intervened and stated where the four patients would be transported. It was later decided among the sending and receiving hospital clinicians on the Clinical Call that it should be a clinician-to-clinician decision. This decision is vastly different from the process to move a single patient. For example, in Region IV, the decision to move the patient from MUSC to EUH was decided jointly by the Georgia Department of Public Health (GA DPH) and the South Carolina Department of Health and Environmental Control (SC DHEC).

Recommendation(s):

- HHS/ASPR should engage HHS RECs and other key patient movement partners—including, but not limited to, RETCs and state health officials—to develop a standard framework for inter-regional HID patient movement coordination. This framework should clearly define the roles and responsibilities of the HHS RECs and federal partners in facilitating coordination, and should allow regions the flexibility to identify, on a region-by-region basis, which regional, state, and local partners will fulfil key coordinating roles.
- HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018) should include guidance on coordinating the movement of patients in a cluster to multiple RETCs. HHS/ASPR should consider reviewing and including information from the *Draft ASPR Highly Infectious Disease Cluster Plan* (December 2015) into the *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018).
- HHS/ASPR should collaborate with local, state, and regional partners to define the process(es) and ultimate decision authority in determining which RETC will receive patients. Following the exercise, participants identified the following three considerations in deciding if a patient should be moved to an RETC and if so, which RETC should receive patients, and recommended that these points be included in local, state, regional, and federal plans: (1) the receiving RETC's bed availability; (2) the patient's preference; (3) the severity of the patient's medical status.

Observation 1.3: Federal and regional HID patient movement plans do not include the timeline for notification, activation, and employment of DOS vendor aircraft(s) in support of domestic HID patient movement.

One of the exercise's artificialities included a time compression in two areas: (1) the time required to request and prepare DOS vendor aircraft to move HID patients; and (2)

the time required to conduct lab testing. During exercise planning, DOS and their vendors indicated that they needed 16 hours' notice to request, staff, load the Containerized Biological Containment System (CBCS), and conduct final preparations of the Boeing 747 aircraft prior to departure from Cartersville, Georgia. Participants identified the need to include this timeline and any other preparatory timelines into patient movement plans.

Recommendation(s):

- Regional and federal patient movement plans should be updated to include the timelines to request, load the CBCS, and conduct other preparatory activities before the Boeing 747 can pick up and transport a HID patient.

Observation 1.4: Facility plans include protocols to successfully minimize the risk of disease spreading to facility staff and others.

The exercise provided originating facilities and RETCs an opportunity to examine their ability to contain the risk of spreading disease while caring for and moving an HID patient. Overall, clinicians that came into contact with an HID patient were familiar with and quickly implemented infection control measures within existing plans.

One facility's plan highlighted a best practice of including detailed information on contractor point of contact information to call for timely terminal cleaning and decontamination services, thereby further minimizing the risk of spreading a HID.

Observation 1.5: Exercise participants identified the need for defined protocols to assist in determining whether a security escort should be used for HID patient transport.

When transporting HID patients, a security escort (e.g., local, state, or federal law enforcement) may be needed to ensure the safety of the patients and transport personnel, as well as the safety of the public. When determining whether or not to use security escorts during the exercise, players considered a variety of factors, including traffic conditions and the presence of media or protestors. Region IV players noted that during the real-world Ebola response in 2014, the high-level of media attention necessitated the use of security escorts. During the exercise, some patients were transported without security escorts, and there were no incidents requiring a law enforcement response. In addition, all partners stated that whenever possible, sirens should not be used during HID transportation to avoid unwanted attention—this situation would change based on traffic conditions or declination of patient condition.

Following the exercise, players in multiple states identified the need to develop formal protocols for determining when a security escort should be used for domestic HID

patient movement. Currently, the EVD patient transport plans for Regions IV, VI, and IX[3] state that it is the responsibility of the HHS REC to coordinate with the sending and receiving states to ensure that a security escort is considered in the process to coordinate transporting a HID patient. The plans do not specify, however, which law enforcement agencies should be used or how the escort should be arranged, if necessary. Also, while the Region X EVD patient transport plan identifies patient security leads for each state, it does not specify how security arrangements should be made.

Recommendation(s):

- Regional HID patient transport plans should define the requirements for a security escort to transport an HID patient and designate a decision authority to determine the use of active, or passive, security.

2. Operational Coordination

Establish and maintain a unified and coordinated operational structure and process that appropriately integrates all critical stakeholders and supports the execution of core capabilities.

Aligned HPP Capabilities: Health Care and Medical Response Coordination

Observation 2.1: Local, state, and federal patient movement partners were not fully knowledgeable on initial notification processes upon receipt of a PUI(s).

During the exercise, some originating facilities and RETCs promptly activated incident command staff to manage internal response operations and coordinate with external partners; but overall, patient movement partners at the local, state, and federal levels expressed uncertainty regarding initial notification processes upon receipt of a PUI(s). In particular, hospitals and public health agencies were uncertain how and when to notify partners about PUIs and patients with a laboratory-confirmed HID.

Recommendation(s):

- Local, state, regional, and federal partners should ensure that HID patient movement plans provide sufficient detail regarding initial notification processes. At a minimum, plans should address the following questions:
  - What are the triggers for notification?
  - What stakeholders should be notified?

[3] *HHS Region IV Ebola Virus Disease Coordination and Transportation Plan* (July 2016) (p. 15); *HHS Region VI Texas, Arkansas, Louisiana, Oklahoma and New Mexico Ebola Virus Disease – Patient Movement Plan* (May 2016) (p. 24); *HHS Region 9 EVD and Other Special Pathogens-Coordination and Transportation Plan* (June 2017) (p. 33).

- How should stakeholders be notified?
- If notification is not received, what are the backup notification procedures?
- Are there special notification procedures for time-sensitive matters?

Observation 2.2: Coordination calls do not align and confusion regarding their purpose, logistics, and timing hampered the ability of providers to focus on patient care.

Over the course of the exercise, approximately 64 multi-agency calls took place to coordinate the movement of seven HID patients. Calls focused on a variety of topics, including, but not limited to: patient care, patient status, transportation logistics, and public communication. The expectation for providers to attend every conference call put pressure on providers to balance patient care requirements. For example, one hospital's first coordination call of the exercise included hospital leadership and medical personnel, which left the emergency department nurses with unanswered questions about how to care for the PUIs. To compound the matter, coordination calls often occurred while providers were at the airport or engaged in patient handoffs, forcing providers to determine how to staff the coordination calls with someone capable of answering questions and someone else equally capable of caring for the needs of the HID patient(s). This resulted in providers not being able to attend coordination calls, causing communication breakdowns and gaps in information sharing among patient movement partners

At the federal level, HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018) describes several conference calls that should take place to coordinate the movement of a HID patient, including the Small Call, Clinical Call, Large Call, Med Call, and multiple logistical coordination calls, each with a different purpose and agenda. However, the coordination calls within HHS's *SOP* do not align with the coordination calls outlined within state and regional plans (e.g., clinical calls in some states occur earlier than what is outlined in HHS's *SOP*). In addition, the exercise revealed that patient movement partners were unclear as to the purpose of some of the federally-led calls (e.g., the difference between and purpose of the Small Call versus the Large Call or the Med Call and the Clinical Call). Therefore, partners were not always prepared to answer questions; key subject matter experts (SMEs) were missing; and the discussion focus diverted to topics not relevant to the particular calls. In addition, the schedule and timeline of federally-led coordination calls were not flexible to ongoing and simultaneously occurring local and state patient care and patient movement coordination activities. The HHS SOC felt pressure to complete pre-identified coordination calls at certain times, and in doing so mistakenly overlapped with other state and local coordination activities.

At the regional level, plans describe communication and coordination processes in varying levels of detail. For example, the Region X plan identifies four conference calls that will take place to facilitate patient movement—a policy call, a clinical call, a logistics call, and a public communication call. For each call, the plan specifies which agencies and organizations will facilitate the call, which specific personnel—by position—from various agencies and organizations will participate on the call, and what outcomes the call should achieve. The Region IV, VI, and IX plans contain flow charts depicting the various steps involved in identifying an RETC, coordinating ground transport, and coordinating air transport; however, these plans do not include specific conference call requirements or outcomes.

Recommendation(s):

- Local, state, regional, and federal partners should include detailed information on all conference calls required to coordinate patient movement across regions, including details related to call facilitation, purpose, participation, and desired outcomes. Information about each call should address the following:
    - Who is responsible for organizing the call (scheduling, sending invitations, providing dial-in information)?
    - Who is responsible for facilitating the call?
    - Who is responsible for participating on the call?
    - What types of information should be shared on the call?
    - What key decisions need to be made on the call?
    - What, if any, outputs should be delivered following the call?
    - When, with respect to other required coordination calls, should the call occur?
- HHS/ASPR should ensure that the schedule and timeline of federally-led coordination calls are flexible and support states and regions.
- HHS/ASPR should consider combining coordination calls and eliminating others in their plans, including the Small Calls outlined within HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018), as the request for an HID MEDEVAC mission and pertinent patient information can be sent via an email to DOS.

Observation 2.3: Patient care providers were uncertain of how and when to initiate direct provider-to-provider communication during the patient transfer coordination process.

Direct provider-to-provider communication is an important element of the inter-facility transfer process, as it provides the sending and receiving patient care teams the opportunity to exchange information about the patient's condition and specific medical

needs. Provider-to-provider coordination calls are a routine part of any inter-facility patient transfer. However, providers were uncertain how and when to engage with one another to share and obtain patient information during the exercise. Confusion arose due to the large number of state, regional, and federal agencies involved in coordinating patient transfer. This was observed in Regions VI and IV, as detailed below.

- Region VI: According to the Region VI EVD patient movement plan, the Texas State Medical Operations Center will coordinate communication between the sending facility and UTMB before a decision to transfer the patient is made.[4] This did not occur during the exercise. The sending facility, and receiving RETC did not communicate directly until the HHS-led Large Call, which took place several hours after the decision to transfer the patient to UTMB had been made. The Large Call was intended to serve as the final coordination call between all local, state, and federal agencies involved in transporting the patient and was not the appropriate forum for providers to engage in a detailed discussion of the patient's history and status. Players agreed that the sending and receiving providers should have discussed patient information at an earlier time, well before the Large Call.
- Region IV: According to the Region IV HID patient movement plan, the Georgia Department of Public Health will coordinate a conference call involving GDPH, the originating state, the sending facility, and receiving RETC to exchange patient information as required for a routine inter-facility patient transfer.[5] During the exercise, the decision to send the patient to the RETC was made without input from the sending facility despite the sending facility's request to be involved in the decision-making and coordination process. Several hours after the decision to send the patient to the RETC had been made, the sending facility was directed to coordinate a clinical call with all involved partners. The sending facility scheduled the call but felt that they should have been engaged earlier in the patient transfer coordination process.

In both Regions VI and IV, the sending providers lacked situational awareness in the early stages of the patient transfer coordination process, and communication between the sending and receiving providers did not occur as outlined in each region's respective HID patient movement plan.[6] This contributed to confusion among patient

[4] HHS. (2016, May.) *HHS Region VI EVD Patient Movement Plan*.
[5] HHS. (2017, June.) *Master Region IV EVD Transportation and Coordination Plan*.
[6] Evaluators noted that state and regional players may have felt pressured by the condensed time frame of the exercise to make quick decisions regarding patient transfer, which may have distracted them from engaging with providers as they would during a real world event.

care providers about—what medical procedures should be performed during the various stages of patient care—including care at the frontline facility, at the assessment facility, and in transit. Players noted that they lacked clear guidance on what treatments to provide. EMS personnel specifically requested guidance on what procedures they should perform on a patient in an ISOPOD and raised concerns about their liability for any actions taken, or not taken, should the patient's condition deteriorate during transport.

Recommendation(s):

- Patient movement partners should ensure that both sending and receiving patient care providers are engaged in the patient transfer decision-making and coordination process, per regional HID patient movement plans.

Observation 2.4: There was confusion among patient movement partners about when it is appropriate to discuss PII on coordination calls.

During the exercise, participants expressed concerns about the amount of patient information being openly shared on coordination calls involving large groups of participants from diverse organizations. Some participants shared PII on the coordination calls, which evaluators noted may have violated the *Health Insurance Portability and Accountability Act of 1996 (HIPAA).* Information shared during the exercise included: patients' full names, weight, vitals, and their medical history. Following the exercise, participants identified the need to ensure that HID patient movement plans specify what information is needed and when PII can be shared.

Recommendation(s):

- HID patient movement should specify when it is appropriate for patient movement partners to discuss PII. HHS RECs should advise local and state partners to consult *HIPAA and Disasters: What Emergency Professionals Need to Know* (September 2017).

Observation 2.5: The FAA provided the HHS SOC with timely flight status updates, allowing ground transport crews to ensure that their equipment and personnel were staged and prepared for patient handoff.

When air transportation is required to move HID patients from U.S. facilities to RETCs, the FAA is responsible for coordinating airspace, validating flight plans, and notifying the SOC of aircraft takeoff and landing.[7] Specifically, HHS's draft *Coordination Flow of*

[7] An overview of the roles and responsibilities of interagency partners are provided at the beginning of HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018).

Patients Infected with Highly Contagious Pathogens SOP (February 2018) specifies that the FAA will notify the SOC when the aircraft departs for and arrives at the sending airfield to pick up patients and also when the aircraft departs for and arrives at the receiving airfield to drop off patients. During the exercise, the SOC requested that FAA provide notifications 10 minutes before aircraft arrival at sending and receiving airfields. FAA fulfilled this request, providing timely notifications of aircraft takeoff, approach, and landing throughout the exercise. The SOC relayed these notifications to HHS RECs, who in turn relayed the notifications to regional, state, and local partners. These flight notifications allowed hospitals and EMS providers to better prepare for patient handoff.

3. Critical Transportation

Provide transportation (including infrastructure access and accessible transportation services) for response priority objectives, including the evacuation of people and animals, and the delivery of vital response personnel, equipment, and services into the affected areas.

Aligned HPP Capabilities: Health Care and Medical Response Coordination; Continuity of Health Care Service Delivery

Observation 3.1: Existing protocols for communication between DOS vendor medical staff and medical staff at sending and receiving hospitals before and during patient transport were insufficient for maintaining situational awareness of the patient during aerial movement.

Under a DOS vendor contract, DOS maintains the exclusive use of two Gulfstream III aircraft configured with Airborne Biological Containment System (ABCS) units and per diem exclusive use of a third Gulfstream III aircraft also configured with an ABCS unit.[8] Under the same contract DOS through a vendor maintains a subcontract relationship with an additional vendor to provide one Boeing 747 aircraft with the ability to be configured with up to two CBCS. When an assessment hospital, other facility, or state requests HHS's assistance in transporting an HID patient to an RETC, HHS will notify DOS, and DOS will contact a vendor for air transportation support. Once air transportation support is secured, HHS will coordinate all details of the movement directly with DOS who will relay that information to their vendor.

During the exercise, the six patients requiring aeromedical transport were successfully delivered to their respective RETCs. However, issues arose due to a lack of

[8] The terms of DOS's contract with their vendors are outlined in HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018).

communication between the DOS vendor and patient care providers before and during patient transport, as detailed below.

- **Before Transport:** During the planning process, HHS identified six mock patients for air transport. Prior to the exercise, DOS and their vendors requested that each patient provide the following information for the flight manifests: full legal name, birth date, birth city, birth state, and their social security number. If the patients were born outside of the U.S., they were required to provide a U.S. issued passport. As this was an exercise, HHS provided this information to DOS and their vendors beforehand and was not requested on any exercise calls. For a real-world patient movement mission, DOS and their vendors should identify what information is needed on each patient prior to transport and the organization/agency required to provide this information.

  Before the patients were transported, patient movement partners participated in several clinical coordination calls to review and validate the patients' conditions and establish a point of contact on each clinical team that would be handling the patients. Clinicians expressed a desire to include DOS vendor medical personnel on these calls, and HHS relayed this request to DOS. However, DOS vendor medical crews were on crew rest and including them on pre-movement coordination calls would break crew rest.

- **During Transport:** According to HHS's draft *Coordination Flow of Patients Infected with Highly Contagious Pathogens SOP* (February 2018), DOS vendor medical personnel will use onboard communication equipment to advise the receiving RETC on the in-flight status of the patient—the update will be relayed from DOS vendor medical personnel to DOS headquarters, from DOS headquarters to the HHS SOC, then the SOC sends this notification to the HHS RECs. However, during the exercise, it was recognized that the ability for the DOS vendor medical personnel to provide in-flight patient status updates does not exist. For example, one patient became "wet" (vomited) during the flight from Boise, Idaho to Spokane, Washington; however, the patient's vital signs did not cause significant concern to trigger a patient status update. DOS vendor medical personnel first informed the receiving EMS crew that the patient's status had changed from "dry" to "wet" when the patient handoff was underway. Following the exercise, the EMS crew noted that they would have taken different precautions had they been informed in advance that the patient had become "wet". Similarly, RETCs re-stated their desire to receive in-flight patient status

updates to help them prepare for patient arrival.[9]

Recommendation(s):

- HHS/ASPR should: (1) collaborate with DOS to develop a formal memorandum of agreement (MOA) describing in detail the roles, responsibilities, logistics and coordination processes required to use DOS vendor resources to move HID patients in support of HHS mission requirements. The MOA should include specific responsibilities and actions to be taken by, HHS/ASPR and DOS; and (2) clarify communication capabilities and protocol to be activated for use during HID patient movement operations. HHS RECs should then socialize the updated plans among state and local HID patient movement partners.
- HHS/ASPR should work with DOS and DOS vendors to define and formalize the patient identification requirements, and include those requirements in any MOA established between HHS/ASPR and DOS.

Observation 3.2: Hospitals and EMS providers were unfamiliar with DOS vendor patient transfer protocols, which hampered their ability to plan for and seamlessly execute patient handoff.

During the exercise, hospitals and EMS providers did not have access to DOS vendor SOPs nor were they provided an opportunity to consult directly with DOS vendor medical personnel before or during the transport coordination process. As a result, air and ground patient transfer protocols were not synchronized, and several challenges arose during patient handoff. These challenges are detailed below.

- **Some EMS crews did not know when or how to approach the DOS vendor aircraft to initiate patient handoff.** EMS crews delivering patients from assessment hospitals to DOS vendor medical crews did not know whether anyone had been assigned to greet them upon their arrival at the airfield. When the crews received no greeting, they sought out the DOS vendor medical safety officer to request guidance on when and how to approach the aircraft to hand off the patients. After the exercise, players noted that DOS vendor medical personnel may have been preoccupied with aircraft tours when the ambulances arrived, which may have prevented them from greeting the EMS crews as they would during a real-world event. Nevertheless, EMS players felt that they should have been provided a point of contact for the DOS vendor and instructions on how to execute the patient handoff before their arrival at the airfield.

[9] During an after-action following between HHS/ASPR and DOS, there are no plans to include this capability in the future.

- **Ground transportation teams were unsure what clinical information, if any, the DOS vendor would provide during patient handoff.** At Ellington Airport in Texas, the DOS vendor transferred a patient to EMS personnel with minimal verbal communication. DOS vendor medical personnel and the patient stood ready on the tarmac next to the aircraft as the ambulance drew near. As soon as the ambulance parked alongside the aircraft, the EMS crew loaded the patient into the ambulance. Within five minutes, the EMS crew secured the patient and departed for UTMB. During their brief interaction with the EMS crew, DOS vendor medical personnel did not provide a clinical update, nor did they pass along any patient care documentation which was sent along with the patient from Norman Regional Hospital.
- **Hospitals and EMS crews were unaware of the DOS vendor PPE requirements for patients.** In one region, DOS vendor medical personnel required the patient to fully doff the sending facility's PPE and don the PPE provided by the DOS vendor before boarding the aircraft. A member of the DOS vendor medical team met the patient at the ambulance to perform this task. Because the transport team was not made aware of this ahead of time, they did not have readily accessible arrangements for a privacy screen or similar means of ensuring patient privacy. Furthermore, the transport team had not anticipated the need to take possession of the patient's doffed PPE and transport it back to the sending facility for disposal.
- **It was not always clear which agency had primary responsibility for patients on the tarmac.** In multiple regions, it was unclear who had primary responsibility for the patient at the airfield after the patient was removed from the ambulance but before the patient boarded the DOS vendor aircraft. This was an issue brought up during the planning process and was also seen in DOS' Tranquil Shift Exercise but no guidance was agreed upon.

Recommendation(s):

- DOS should consider providing their vendor patient transfer SOP to hospitals and EMS providers to allow them to align their protocols. Before patient transport, all parties that will be involved in handling the patient(s) should review applicable patient transfer protocols including what entity has responsibility of the patient at each point during movement.
- Hospitals, EMS providers, and the DOS vendor should ensure that their patient transfer SOPs specify when and how clinical updates should be provided, as well as how patient care documentation should be handled during transport and multiple handoffs.

Observation 3.3: Improper ambulance preparation compromised patient health and safety.

To protect an ambulance from contamination during HID patient transport, EMS personnel commonly apply clear plastic sheets to all surfaces within the ambulance's patient compartment, including the ceiling, walls, floor, and benches. According to national ambulance preparation guidelines developed by the HHS/ASPR Technical Resources, Assistance Center, and Information Exchange (TRACIE), EMS personnel should cut holes in the plastic sheets for ventilation ports to allow proper air flow.[10] During the exercise, EMS personnel did not cut holes in the plastic sheets applied to the ambulance that was used to transport the pediatric patient. As a result, the patient compartment became very warm during transport. The heat and lack of air flow caused the pediatric patient to suffer an anxiety attack during the hour-long trip causing the patient and his guardian to request immediate release from the ambulance. It took several minutes for the transport crew to identify a safe place for the ambulance and convoy of approximately 15 escort vehicles to make an emergency stop. Once calm, the pediatric patient refused to re-enter the ambulance and was transported in an escort vehicle for the remainder of the trip.

Improper ambulance preparation caused issues in other instances as well. The ambulances used to transport two other patients were also draped in plastic sheets that blocked the ambulance's air vents, causing the patient compartment to become uncomfortably warm during transport. The heat in the patient compartment on these moves was not severe enough to require an emergency stop for either ambulance; however, EMS personnel noted that more serious consequences could have arisen if it were a hotter day. Additionally, the plastic sheets blocked access to seatbelts.

Patient movement partners learned several lessons from these experiences. First, transport crews identified the need to ensure that any measures taken to protect the ambulance from contamination do not interfere with ventilation or compromise patient safety. Second, patient movement partners identified the need to develop protocols for emergency stops during transport. The convoy transporting the pediatric patient was able to find a safe place to stop but players noted that pre-identified sites for potential stops along the route would have been helpful.

Recommendation(s):

- EMS agencies should ensure that any measures taken to protect the ambulance from contamination—such as the application of plastic sheets or impermeable

[10] HHS/ASPR/TRACIE. (2017, June). The *EMS Infectious Disease Playbook*. Retrieved from https://www.ems.gov/pdf/ASPR-EMS-Infectious-Disease-Playbook-June-2017.pdf

barrier cloth to interior surfaces—do not compromise patient health and safety.

- EMS agencies should consider developing protocols for emergency stops during transport. These protocols should describe the conditions under which an emergency stop may be necessary and should include procedures for identifying potential sites along the transportation route.

Observation 3.4: Patient movement partners successfully implemented a variety of technologies—including livestreaming, videoconferencing, and GPS tracking—to prepare providers to receive the patient(s) and enhance situational awareness during patient transport.

During the exercise, Region IX patient movement partners used various technologies to share information about each patient's location and condition during transport. For example, a mobile command post was established at Los Angeles International Airport with livestreaming capabilities. Personnel at the mobile command post used a secure link to share the livestream with local, state, and federal partners, who were able to watch the aircraft land and offload the patients in real time. While the ambulances were en route to CSMC, EMS personnel used tablets to videoconference with the receiving clinicians and provide patient status updates. EMS personnel also shared their location with the receiving clinicians using a mobile GPS tracking application which helped the clinicians determine when to begin donning PPE. Following the exercise, Region IX patient movement partners, as well as other participating Regions, agreed that there are significant benefits to using GPS to closely monitor the movement of the ambulances carrying HID patients in order to ensure the patient offloading area is adequately prepared to receive the patient and clinicians are able to don their PPE in a timely manner. Additionally, Region IX patient movement partners agreed that they will continue to using livestreaming, videoconferencing, and GPS tracking for future HID patient movement operations.

Observation 3.5: "High risk" ambulances enhanced the safety and efficiency of HID patient transport.

California's Emergency Medical Services Authority (EMSA) used the exercise as an opportunity to conduct its first test of newly acquired "high risk" ambulances, which have special features that make them ideal for HID patient transport. The patient compartment of "high risk" ambulances is constructed entirely from metal and plastic, allowing for easy decontamination. Additionally, the patient compartment has its own air flow, completely separate from the driver's compartment. During the exercise, EMS personnel implemented a communications system that allowed for easy communication between the separate compartments. Overall, Region IX patient movement partners

deemed the test of the "high risk" ambulances a success. Although EMSA personnel who rode in the "high risk" ambulances reported being too cold due to the ventilation system, this was a positive finding, as EMSA had experienced issues with overheating in the past when using traditional ambulances.

4. Logistics and Supply Chain Management

Deliver essential commodities, equipment, and services in support of impacted communities and survivors, to include emergency power and fuel support, as well as the coordination of access to community staples. Synchronize logistics capabilities and enable the restoration of impacted supply chains.

Aligned HPP Capabilities: Continuity of Health Care Service Delivery

Observation 4.1: The lack of standardized PPE requirements across the country resulted in various, inconsistent techniques being utilized posing challenges throughout patient movement operations.

Currently, there is no universally accepted PPE standard for treating and transporting HID patients for providers, patients, and for family members accompanying patients. Similarly, no protocol exists that outlines the conditions for transporting HID patients in an ISOPOD versus PPE. The following sections address these gaps as seen during the exercise.

- **Clinicians applied varied, inconsistent criteria in determining whether an ISOPOD should be used for inter-facility transport of HID patients.** There is currently no guidance at the regional or federal levels on how to decide whether an ISOPOD should be used during inter-facility transport of EVD patients. During the exercise, it was revealed that the criteria used to determine whether ISOPODs should be used to transport HID patients vary on a clinician-to-clinician basis. When determining whether to use ISOPODs during the exercise, clinicians considered the following interrelated factors:
  - **Patient condition:** Some clinicians took the position that ISOPODs should only be used to transport "wet" patients—that is, patients in progressed stages of EVD with symptoms of vomiting, diarrhea, and, in some cases, internal and external bleeding.[11] Other clinicians cautioned that "dry" patients could become "wet" during transport and therefore took the position that ISOPODs should be used in all cases. In addition, clinicians considered the ability of their "dry" patient to ambulate when deciding whether to use an

[11] World Health Organization. (2017). *Frequently Asked Questions on EVD.* Retrieved from http://www.who.int/csr/disease/ebola/faq-ebola/en/

ISOPOD. In this case because the patient was able to ambulate over short distances, the decision was made to transport the patient in PPE, rather than in an ISOPOD.

- **Ambulance configuration:** One hospital in consultation with NETEC considered the configuration of the ambulance as a major determining factor in their decision on the use of an ISOPOD. They determined that if the ambulance interior was appropriately wrapped and the patient was “dry” then the patient could be safely transported in PPE vice an ISOPOD.
- **Resource scarcity:** Most hospitals and EMS providers involved in the exercise own only one or two ISOPODs, if any. Some clinicians therefore questioned whether it would be prudent to use an ISOPOD for a “dry” patient, when a “wet” patient, with greater need, could require it at a later time. Players noted that their level of concern about conserving ISOPODs would depend, in part, on the scope of the outbreak.

- **Full body PPE made it challenging to identify and differentiate between the various personnel involved in patient care and transport.** During the exercise, hospital and EMS personnel wore a similar assortment of PPE, which commonly consisted of impermeable coveralls, gloves, boot covers, and powered air-purifying respirators (PAPRs). Some personnel also wore aprons. The extensive assortment of PPE completely covered the individuals’ bodies and partially covered their faces, making it challenging to differentiate between personnel and discern their roles, particularly when multiple personnel belonging to different teams were involved in handling the patient.

  Players cited several reasons why the inability to differentiate between personnel wearing PPE can be problematic. First, confusion about individuals’ roles can hamper communication and coordination between teams. Second, not being able to differentiate between individuals impedes the ability of safety officers and trained observers to monitor individuals and quickly command their attention, should a safety issue arise. Third, while unlikely, outsiders could disguise themselves in PPE to gain unauthorized access to a facility.

  In an effort to make it easier to identify personnel wearing PPE, patient care teams in Regions IX and X wrote each team member’s name on the back of his or her PPE with permanent marker, along with the time at which the PPE was donned. Other teams identified this as a best practice as well.

- **Patient movement partners encountered challenges managing the health risks posed to and by the pediatric patient’s accompanying parent.** During

the exercise, the pediatric patient in Region VI had mild symptoms, and patient movement partners made the decision to allow the parent to accompany the patient during transport from CHI St. Luke's Health–The Woodlands Hospital to TCH. Over the course of the exercise, concerns arose regarding (1) management of the parent's PPE, and (2) differences in the sending and receiving facilities' protocols regarding parental access to the isolation unit.

During transport to TCH, the parent rode in the ambulance with the patient wearing a gown, gloves, and surgical mask. However, this level of PPE may not have provided adequate protection for the parent. Also, it was not clear who was responsible for assisting the parent in doffing his PPE. Upon arrival at the receiving facility, the parent was permitted to enter the hospital while still wearing the PPE donned at the sending facility, raising concerns about contamination.

Although the sending facility allowed the parent to enter the isolation unit with the patient, the parent was not allowed in the isolation unit at the receiving facility. Given the variation in hospital protocols regarding parental access to the isolation unit, patient movement partners identified the need to review the receiving facility's protocols early in the transportation coordination process to set expectations for the parent and the minor patient.

- **Select PPE components posed safety risks for healthcare personnel.** During the exercise, many healthcare facilities implemented effective practices in PPE management. For example, healthcare facilities across all four participating HHS regions implemented "buddy" systems to don and doff PPE, which was particularly helpful when doffing PAPRs. At CSMC, a large printed flip book was used to guide healthcare workers as they doffed each piece of PPE in a step-by-step process.

  In addition to aforementioned best practices, hospital and EMS personnel also identified the following PPE-related issues during the exercise:
  - Tyvek® boot covers were susceptible to tearing when worn on rough outdoor surfaces. Responders noted that objects such as rocks or the grated steps of the DOS vendor aircraft could easily cause a rip or tear in boot covers.
  - Some responders wore two sets of boot covers—the first set was integrated into their coveralls and the second set was worn over the first. This double layering decreased traction and increased the risk of slipping on smooth surfaces.
  - Tape used to secure PPE was responsible for tears during the doffing process. Healthcare personnel noted that the risk of tears due to tape may correlate with the thickness of the tape used, with thicker tape presenting a

greater risk.

- One patient care provider wearing a PAPR experienced light headedness, which may have occurred because the PAPR had been secured too tightly.

Recommendation(s):

- HHS should consider developing guidelines to help clinicians determine when to use an ISOPOD during inter-facility transport of HID patients. These guidelines should be incorporated into regional, state, local, and facility plans, as applicable.
- HHS should consider working with hospitals, EMS providers, and state public health agencies should to develop PPE protocols for parents or guardians who accompany pediatric HID patients during inter-facility transport. Protocols should specify the level of PPE required for the parent or guardian at each stage of the transport process, and identify who is responsible for ensuring that the parent or guardian safely dons and doffs his/her PPE.
- If a pediatric HID patient will be accompanied by a parent or guardian during transport, the parent or guardian should be notified prior to transport whether entry into the isolation unit will be permitted by the receiving and/or sending facility.
- Hospitals and EMS providers should consider exploring methods to easily and readily identify personnel wearing PPE. The chosen method of identification should convey, at minimum, the individual's name and organization.
- Hospitals and EMS providers should consider assessing the suitability of PPE for various indoor and outdoor settings and explore options to mitigate potential hazards (e.g. slippage or tearing).
- Hospitals and EMS providers should consider maintaining an adequate inventory of appropriately-sized PPE and ensure that all responders are properly fitted in advance of an incident.

Observation 4.2: Hospitals and EMS providers were well-supplied with PPE for their personnel and patients.

During the real-world Ebola epidemic of 2014-2016, healthcare staff in U.S. facilities identified the lack of sufficient PPE as an issue. [12] Since then, healthcare facilities have taken steps to stockpile PPE based on their facility's level of risk. As such, all of the hospitals and EMS providers involved in the exercise had sufficient PPE to protect their personnel and patients. Facilities stored their PPE in easy-to-access locations and had a variety of sizes of various PPE components. While existing stores of PPE were sufficient for the exercise, participating organizations were unsure how a larger-scale outbreak would impact the national PPE supply chain.

Observation 4.3: Some facilities do not routinely inspect equipment required to care for and transport HID patients.

The exercise underscored the importance of regular equipment inspections, as some facilities experienced issues with equipment that had been infrequently used and was no longer in working condition. For example, at one hospital, clinicians discovered during the exercise that some equipment in their isolation unit was no longer fully functional. To prevent this from happening in the future, clinicians identified the need to add equipment inspections to their HID patient preparation checklist, which will include checking the expiration dates on PPE and batteries.

Recommendation(s):

- Hospitals and EMS providers should consider developing protocols for routine inspection of all equipment and supplies required to care for and transport HID patients.

Observation 4.4: Mock ZMapp™ vials were successfully deployed to RETCs but experienced minor travel delays, shipment errors, and dosage miscalculations.

ZMapp™ is an experimental drug being developed by Mapp Biopharmaceutical (hereafter referred to as "Mapp Bio") to treat patients with EVD.[13] During the exercise, all participating RETCs requested mock ZMapp™ vials from Mapp Bio for the purpose of assessing the timeliness of the delivery as well as the ability of clinicians to prepare and administer the drug. While some RETCs received the mock vials without any issues, others experienced minor delays. RETCs had been informed that delivery of ZMapp™ would take no longer than 24 hours; however, delivery of the mock ZMapp™

[12] Independent Panel on the HHS Ebola Response. (2016, June). *Report of the Independent Panel on the HHS Ebola Response*. Retrieved from https://www.phe.gov/Preparedness/responders/ebola/EbolaResponseReport/Documents/ebola-panel.pdf
[13] For more information about ZMapp™, see http://mappbio.com/zmapp-faq/.

vials from a Mapp Bio facility in New Jersey to PSHMC in Washington State took approximately 30.5 hours due to a 20-hour layover in Utah. The delivery of mock vials to CSMC in California also took longer than expected because the numbers in the street address had been transposed. The package was re-rerouted to CSMC, but the total delivery time was approximately 22 hours. RETCs and Mapp Bio identified the need to ensure that the ZMapp™ courier is provided accurate shipping information and also to closely monitor the shipments to identify and address any potential causes for delay.

In addition, multiple RETCs noted that they did not receive enough mock ZMapp™ vials to treat their patients; however, this issue stemmed from an exercise artificiality. The mock vials had been pre-ordered—a practice not done in a real-world situation—to ensure that they would arrive at the RETCs within the exercise's compressed timeframe. During the exercise planning process, the mock patients provided HHS planners with their weights which were then used to place the orders prior to the exercise. Some of the patients' weights were slightly off from their actual weights taken during the exercise causing the quantity of mock vials to be less than what was required to treat the patients. Although an exercise artificiality, Mapp Bio recognized that they may be provided inaccurate patient weights and agreed as a best practice to send more vials than necessary.

Despite issues with the delivery and quantity of the mock ZMapp™ vials, preparation and administration of the drug went smoothly at each of the RETCs. Through HHS/ASPR's coordination and partnership with NETEC, the exercise successfully activated clinical research protocols for medical countermeasures. Clinicians appreciated the opportunity to exercise their ZMapp™ protocols.

Recommendation(s):

- Mapp Bio should consider decreasing shipment times to mitigate potential travel delays or shipment errors.
- RETCs should consider refining their ZMapp™ protocols based on feedback provided by NETEC evaluators.

5. Public Health, Healthcare, and Emergency Medical Services

Provide lifesaving medical treatment via Emergency Medical Services and related operations and avoid additional disease and injury by providing targeted public health, medical, and behavioral health support, and products to all affected populations.

Aligned HPP Capabilities: Health Care and Medical Response Coordination; Continuity of Health Care Service Delivery; Medical Surge

Observation 5.1: Patient care teams quickly implemented procedures to monitor personnel who had direct contact with HID patients.

During the exercise, several hospitals demonstrated that they are well-prepared to conduct personnel monitoring. At EUH, for example, all personnel recorded their baseline temperatures before entering the isolation unit with the patient and continued to check and record their temperatures at regular intervals using an electronic system accessible by hand-held devices. At MUSC, hospital personnel reported that they use a similar computer-based monitoring system to ensure they do not become infected as well.

Observation 5.2: Hospitals successfully and safely collected, packaged, and simulated shipment of patient specimens to state public health laboratories for testing.

During the exercise, hospitals quickly contacted their state health departments to report suspicion of Ebola. In consultation with state epidemiologists, all hospitals determined laboratory testing was required to confirm their suspicions. Overall, the collection, packaging, and simulated shipment of patient specimens went smoothly, with hospitals noting only minor areas for improvement with respect to infection control and packaging techniques. In Region X, state public health officials praised Saint Al's staff for their expert handling of the PUIs' specimens, noting an improvement upon performance during previous drills. In Region VI, there was a slight delay in identifying a courier for the specimen from CHI St. Luke's Health–The Woodlands Hospital, but partners ultimately determined that the Bureau of Laboratory Services of the Houston Health Department would send a courier to retrieve the specimen for testing.

Observation 5.3: Inclement weather affected the ability of EMS personnel to don and doff PPE at airfields and increased the risk of contamination during patient handoff between EMS providers and the DOS vendor.

The exercise highlighted the need to take inclement weather into consideration when selecting a handoff location, as exceptionally windy conditions in Regions VI and IX

hampered the ability of EMS and DOS vendor personnel to safely conduct patient handoff.

At the Will Rogers World Airport in Region VI, EMS and DOS vendor crews faced winds of 30 to 40 miles per hour as they unloaded the patient from the ambulance onto the tarmac; removed her from the ISOPOD; and helped her don a gown, gloves, boot covers, and surgical mask provided by the DOS vendor. As the patient and a member of the DOS vendor medical crew began to board the aircraft, a surgical mask—possibly belonging the patient—blew off onto the tarmac. Similarly, at Los Angeles International Airport in Region IX, a patient's surgical mask was blown off as he was being offloaded from the aircraft. Both of these incidents were concerning to players, as loose PPE on the tarmac can cause costly and potentially life-threatening damage if ingested by jet engines. Additionally, dirty PPE carried by wind poses a danger to unprotected bystanders.

Although dry weather conditions allowed EMS personnel to don and doff PPE in the open air, EMS crews identified the need to identify alternate locations for donning and doffing in case of precipitation or other inclement weather. EMS crews also discussed the possibility of erecting temporary shelters at the airfield during inclement weather.

Recommendation(s):

- Ground and air ambulance teams, together with airport officials, should consider identifying alternate locations for donning and doffing of PPE and patient handoff at the airport to provide protection from inclement weather.

CONCLUSION

The 2018 Tranquil Terminus FSE provided an opportunity for HHS to examine the nation's capability to conduct domestic HID patient movement operations in coordination with local, state, regional, federal, private sector, and NGO patient movement stakeholders. With over 50 participating organizations, the Tranquil Terminus FSE became the largest patient movement exercise in HHS history.

The exercise revealed several strengths and areas for improvement in domestic HID patient movement operations. Notably, patient movement partners successfully followed existing protocols and implemented measures to minimize the risk of spreading disease; used innovative technologies to enhance situational awareness and better prepare providers for receipt of the patient; and, despite communication and coordination challenges, proactively sought answers regarding transportation logistics and coordination activities. Conversely, the exercise revealed a number of areas for improvement, including gaps in and discrepancies among local, state, regional, and federal HID patient movement plans, understanding the DOS vendor's roles and responsibilities, as well as challenges in coordinating inter-regional patient movement activities, implementing coordination conference calls, and using PPE.

To address these areas for improvement, HHS/ASPR should engage local, state, regional and federal HID patient movement partners in more deliberate planning on the processes involved in moving multiple HID patients across HHS regions and implementing coordination conference calls. HHS/ASPR should coordinate with DOS to ensure HID patient movement partners understand the DOS vendor's patient transfer protocols and their overall roles and responsibilities in the patient movement process.

Overall, the Tranquil Terminus FSE afforded participants an opportunity to improve their understanding of roles, responsibilities, and capabilities, as well as enhance their ability to safely and security transport HID patients from healthcare facilities within the U.S. to designated RETCs.

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APPENDIX A: EXERCISE DESIGN LESSONS LEARNED

The Tranquil Terminus FSE provided an opportunity to identify lessons learned that should be considered when designing any future full-scale HID patient movement exercises with a wide array of local, state, federal, private sector, and NGO partners. The following lessons learned are based on observations made by exercise control and evaluation staff, as well as feedback from players:

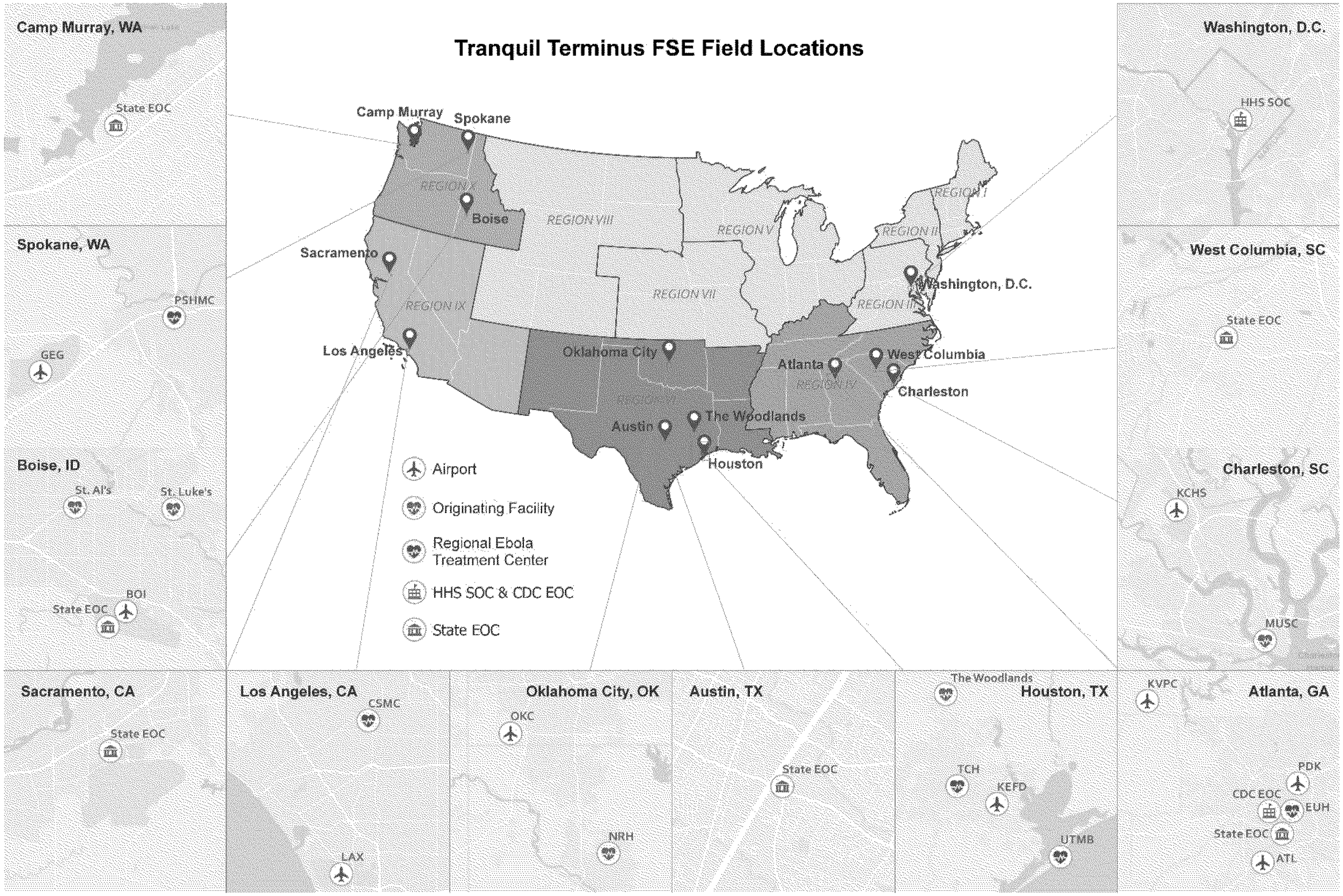
- Mock patient data should be developed to sufficiently address all participating organizations' clinical information requirements. The patient data cards used during the Tranquil Terminus FSE provided helpful information about the patients' symptoms, but did not address the full range of questions asked by healthcare providers throughout the various stages of patient transport. To fill the gaps, players invented patient data during the exercise, which gave rise to conflicting accounts of the patients' histories and symptoms. To avoid this issue in the future, participants recommended developing a complete history and physical examination for each patient based on real-world cases.
- Early in the exercise planning process, the Planning Team recognized that the multiple regional, state, and local plans for HID patient movement had not been thoroughly cross-walked or synchronized and thus had overlapping and redundant requirements as well duplicative actions. In an effort to alleviate these issues, the Planning Team opted to include process flow and expected player actions in the exercise Master Scenario Events List (MSEL). This process allowed the exercise planning group to walk through their plans and processes on a regional level and to identify and resolve issues regarding plan synchronization. This approach led to significant improvement and updates in the various regional, state and local plans prior to exercise conduct. At the end of the exercise planning process, the MSEL represented a very accurate description of the HID patient movement process at all levels, becoming in fact a document akin to an execution matrix. This process was highly praised across the planning team as productive and beneficial to plan improvement. The downside of using the MSEL in this manner was that some players obtained the MSEL and sought to use it as script during the exercise, rather than taking action as they would during a real-world event in accordance with their written plans. This caused confusion among players who didn't have access to the MSEL and may have compromised the evaluation of some activities. Although HHS/ASPR

Lead Planners expressly advised all members of the Planning Team that the MSEL was intended for use only by exercise planners and control cell staff, and that the exercise time compression expressed in the MSEL did not match the written plans, the large number of individuals involved in the exercise made it difficult to control distribution of the MSEL and ensure that its purpose as a control and evaluation tool was universally enforced.

- During the Tranquil Terminus FSE, observers were provided the opportunity to tour the Gulfstream III and Boeing 747 aircrafts used to transport the exercise patients. During these tours, observers—which included medical professionals, emergency responders, student groups, community leaders, and members of the media—learned about the onboard biocontainment units designed specifically for air transport of highly contagious patients. Observers greatly appreciated this educational opportunity, and exercise staff recommended providing similar opportunities to select audiences during future exercises, when feasible.
- During the exercise planning process, HHS planners had to build in artificialities regarding time compressions (i.e., laboratory confirmations from state labs as well as CDC; the time to request DOS vendor assets; and shipping of ZMapp™) in order to keep the exercise on schedule and support local and state organizations' timeline for exercise play. As such, laboratory confirmations were simulated and CDC's *Ebola 72 Hour Communications Plan* and *72 Hour CDC Action Plan* were not exercised or included as part of the exercise objectives.[14] In addition, HHS planners provided Mapp Bio with destination RETC's addresses, desired arrival dates, and patient weights prior to the start of the exercise in order to ensure that ZMapp™ vials reached RETC's during exercise play.

[14] During the identification, management, and transport of HID Persons Under Investigation (PUI), the CDC consults with local, state, and other federal partners. The CDC roles and responsibilities include consultation and coordination with local hospitals, the State Health Department, and HHS for: the differential diagnosis, lab specimen collection, packaging, shipment, testing, and reporting, infection control guidance for healthcare workers, PPE guidance and recommendations, risk communications, and public health messaging. Once confirmed, *the CDC Ebola 72 Hour Communications Plan* and *72 Hour CDC Action Plans*, or a revised version, would go into effect.

APPENDIX B: TRANQUIL TERMINUS FSE FIELD LOCATIONS



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APPENDIX C: IMPROVEMENT PLAN (TO BE COMPLETED)

Core Capability	Observation	Corrective Action	Primary HHS Component Responsible	Implementation Timeline	Priority

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APPENDIX D: PARTICIPATING ORGANIZATIONS

Participating Federal Departments and Agencies
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Preparedness and Response
Immediate Office
Office of Emergency Management
Office of Policy and Planning
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
Office of Public Health Preparedness and Response
Office of Infectious Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Division of Preparedness and Emerging Infections
Division of Global Migration and Quarantine
U.S. Department of State
U.S. Department of Transportation
Federal Aviation Administration
Participating Federal Departments and Agencies
California
California Department of Public Health
California Emergency Medical Services Authority
California Governor's Office of Emergency Services
City of Los Angeles Emergency Management Department
Los Angeles County Department of Public Health
Los Angeles County Emergency Medical Services Agency
Los Angeles World Airports

Georgia
Georgia Department of Public Health
Grady EMS
Idaho
Ada County Paramedics
Central District Health Department
Idaho Department of Health and Welfare
Idaho Division of Public Health
Oklahoma
Oklahoma City Emergency Medical Services Authority
Oklahoma State Department of Health
Oklahoma Regional Medical Response System
South Carolina
South Carolina Department of Health and Environmental Control
Texas
Galveston County Public Health
Harris County Public Health
Houston Airport System
Public Health Authority City of Houston
Public Health Authority Harris County
South-east Texas Regional Advisory Council
Texas Department of State Health Services
Washington State
Region 9 Healthcare Coalition
Spokane Regional Health District
Washington State Department of Health
Participating Non-Governmental Organizations
National Ebola Training and Education Center

Participating Private Sector Organizations
American Medical Response
Fallon Ambulance Service
RETCs
Cedars-Sinai Medical Center
Emory University Hospital
Providence Sacred Heart Medical Center and Children's Hospital
Texas Children's Hospital
University of Texas Medical Branch at Galveston
Originating Facilities
CHI St. Luke's Health–The Woodlands Hospital
Medical University of South Carolina
Normal Regional Hospital
Saint Alphonsus Regional Medical Center
St. Luke's Regional Medical Center
Regional and International Airports
Boise Airport
Cartersville Airport
Charleston International Airport
DeKalb-Peachtree Airport
Ellington Airport
Hartsfield-Jackson Atlanta International Airport
Los Angeles International Airport
Spokane International Airport
Will Rogers World Airport

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APPENDIX E: ACRONYMS AND ABBREVIATIONS

Acronym	Meaning
ABCS	Airborne Biological Containment System
ASPR	Office of the Assistant Secretary for Preparedness and Response
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CSMC	Cedars-Sinai Medical Center
DCDC	Division of Communicable Disease Control
DOS	U.S. Department of State
ED	Emergency Department
EMG	Emergency Management Group
EMS	Emergency Medical Services
EMSA	Emergency Medical Services Authority
EPO	Emergency Preparedness Office
ESF	Emergency Support Function
EUH	Emory University Hospital
EVD	Ebola Virus Disease
FAA	Federal Aviation Administration
FOUO	For Official Use Only
FPO	Field Project Officer
FSE	Full-Scale Exercise
HHS	U.S. Department of Health and Human Services
HID	Highly Infectious Disease
IDHW	Idaho Department of Health and Welfare
MCB	Mission Coordination Branch
MOA	Memorandum of Agreement
MSEL	Master Scenario Events List

Acronym	Meaning
MUSC	Medical University of South Carolina
NETEC	National Ebola Training and Education Center
NGO	Non-Governmental Organizations
OEM	Office of Emergency Management
PAPR	Powered Air-Purifying Respirator
PII	Personally Identifiable Information
PPE	Personal Protective Equipment
PSHMC	Providence Sacred Heart Medical Center
PUI	Person Under Investigation
REC	Regional Emergency Coordinator
RETC	Regional Ebola Treatment Center
SOC	Secretary's Operations Center
SOP	Standard Operating Procedure
TCH	Texas Children's Hospital
TRACIE	Technical Resources, Assistance Center, and Information Exchange
UTMB	University of Texas Medical Branch